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Dear Sir or Madam:

In accordance with 40 CFR 716.30, the International Isocyanate Institute (III) on behalf of its members (BASF Corporation, Dow Chemical Company, ICI Americas, Inc., Miles, Inc. and Olin Corporation) hereby provides a copy of the following recently completed health and safety report (review).

"Review of TDI Toxicity Studies"

Very truly yours,

R. K. Rigger
Managing Director

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REVIEW OF TDI TOXICITY STUDIES

BY

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FOR

THE INTERNATIONAL ISOCYANATE INSTITUTE

REVIEW OF TDI TOXICITY STUDIES

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REVIEW OF TDI TOXICITY STUDIES

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REVIEW OF TDI TOXICITY STUDIES

1 INTRODUCTION

This is a review of all the available TDI toxicology studies taken from the International Isocyanate Institute data base (March 1993). The contents are divided into sections each reporting on an area of toxicology. Within each area, reports of studies from industry sources and from the scientific literature are assessed. The design and results for each study are summarised in the Harmonised Electronic Data Set (HEDSET) format on the attached forms. An evaluation of each study is presented in the text of the review and a summary for each area of TDI toxicology is also described.

The purpose of this comprehensive review is that a) it brings together all the available toxicological information on TDI in its various forms b) it gives easy access to the most important information on each study where sufficient details are available c) it provides a summarised assessment for each area of TDI toxicology d) it indicates areas of toxicology where further information may be required e) it provides a basis for the overall toxicological evaluation of TDI, f) it provides background data for risk assessments for TDI uses and g) it is in a format which can be updated easily and quickly.

TDI has been tested either in the mixed isomer form or as the individual 2,4- or 2,6-isomers. It is important therefore, to note the test substanc used in the descriptio. of each study. Commercially, TDI is usually produced and used as the 80:20, 2,4-:2,6- isomer ratio. This is the isomer mixture tested in many of the toxicity studies. It is nominated as the prescribed test substance (CAS No. 26471-62-5) for the purposes of the HEDSET entry. It is a colourless pale yellow liquid at room temperature and has a pungent odour. The physico-chemical data for the mixture are listed in Section 2 of the HEDSET.

The review covers a comparatively long time scale of testing, approximately 40 years, therefore, the quality of the studies is somewhat variable and attention will be drawn to the more rigorous tests and reliable results in the summaries for each area of toxicology.

2 ACUTE ORAL TOXICITY (Study Nos.A1-A4)

2.1 Summary

The studies, reviewed below, consistently show that TDI, either as the 2,4 isomer or as an isomer mixture, has low acute oral toxicity in rodents with LD_{50}s in the range 4000-6000 mg/kg.

2.2 Study Assessments

The acute oral toxicity of TDI in various forms has been assessed in three rat and one mouse study.

In Study A1, undiluted 2,4-TDI was given by stomach tube to rats at 6 dose levels and the acute oral LD_{50} was estimated to be 5800 mg/kg.

In Study A2, groups of male rats were dosed orally with TDI, as 'mixed isomers', at levels up to 10,000 mg/kg and then observed daily for up to 14 days. Clinical effects were apparent at 1000 mg/kg and were pronounced in all animals at 10,000 mg/kg. The acute oral LD_{50} was calculated to be 5840 mg/kg.

In Study A3, groups of rats were given doses of TDI (80:20 isomer ratio) up to 14,700 mg/kg, followed by a 14-day observation period. Clinical effects were noted at the higher doses and acute oral LD_{50}s were determined to be 5110 mg/kg in males and 4130 mg/kg in females.

Study A4 was undertaken to the same design as study A3, using mice as test animals with dose levels up to 10,000 mg/kg. No clinical signs were seen. The acute oral LD_{50}s were 4130 mg/kg in males and 5620 mg/kg in females.

3 ACUTE INHALATION TOXICITY (Study Nos.B1-B12)

3.1 Summary

The reported acute inhalation testing of TDI covers a variety of study designs. The results are summarised in Table 3.1. These show that the rat 1h-LC_{50} for the 80:20 isomer ratio is between 66 and 85ppm in 2 separate studies. There is also good comparison for the results for the 4h-LC_{50} in another two rat studies at 15.2 ppm and 13.9 ppm. Results in the other species studied are comparable though slightly lower.

The signs of acute toxicity include nasal irritation, laboured breathing, lachrymation, salivation and general discomfort. Pathological examination showed the lung and trachea to be target organs. Respiratory rate was decreased in the mouse.

3.2 Study Assessments

Several acute inhalation toxicity studies have been undertaken, mainly on the rat but also in other species. All forms of TDI have been involved.

The details for Study B1 are minimal; 600 ppm 2,4-TDI was stated to be lethal to rats and 60 ppm as non-lethal over 6h.

Study B2 was a comprehensive assessment; groups of 4 male and 4 female rats were exposed to concentrations of TDI (80:20 isomer ratio) from 17.4 to 267 ppm for one hour and then observed for 14 days. Clinical signs were seen in an exposure related manner at all levels. The acute one hour inhalation LC_{50} was estimated to be 66 ppm.

Study B3 had a basic design, 10 male rats were exposed to a single concentration of 0.25 ppm TDI (unspecified form) for 8h, followed by a 14-day observation period. Apart from slight-moderate erythema during the exposure period there were no other effects.

Study B4 was set up as a preliminary dose range-finding study for TDI, specified as 'mixed isomers'. Groups of 6 rats were exposed to concentrations from <1 to 13.5 ppm for 6h. Effects were noted at all exposure levels, slight at 1 ppm. Fifty per cent mortality occurred at the two higher levels of 4 and 13.5 ppm.

Studies B5 & B6 were carried out to similar designs in order to determine the 1h and 4h LC_{50}s respectively. Groups of 20 male rats were used and were observed for 14 days following exposure to TDI aerosol. Exposure dependent mortality was observed from 0.173 to 2.58 mg/litre from the 1h exposure and from 0.057 to 0.72 mg/litre for the 4h exposure. The 1h-LC_{50} for TDI (80:20 isomer ratio) was determined to be 0.61 mg/litre (85 ppm) and the 4h-LC_{50} as 0.11mg/litre (15.2 ppm).

Studies B7-B10 cover 4h aerosol exposures on 4 species, rat, mouse, guinea pig and rabbit respectively. Each study was undertaken in 2 parts. Firstly, an estimation of mortality over an exposure range of 0.1-34 ppm TDI (unspecified form). Secondly, a pathology assessment of the respiratory tracts up to 28 days after exposure to 2,5 or 10 ppm TDI. In each species, clinical signs included lachrymation, salivation and general discomfort, proportional to exposure concentration. The 4h-LC_{50}s were determined to be 13.9 ppm (rat), 9.7 ppm (mouse), 12.7 ppm (guinea pig) and 11 ppm (rabbit). In each species there was only a limited effect in the lung at 2 ppm but 5 and 10 ppm produced severe effects in lung and trachea.

Two studies were undertaken to evaluate the acute effect on respiratory rate in the mouse. In Study B11, male mice were exposed to 2,6-TDI at concentrations of 0.05-1.1 ppm for 3h. Respiratory rate decreased in a concentration dependent manner over the exposure period. The RD_{50} (concentration required to reduce respiratory rate by 50%) was 0.26 ppm. In Study B12, mice were exposed to 2,4-TDI for 4h in a study of a similar design. The RD_{50} was determined to be 0.199 ppm.

Table 3.1

Acute Inhalation LC_{50} values

Species	Exposure Period (h)	TDI Form	LC_{50} (ppm)	Study No.
Rat	1	8 : 20	66	B2
Rat	1	80 : 20	85	B5
Rat	4	80 : 20	15.2	B6
Rat	4	Unspecified	13.9	B7
Mouse	4	Unspecified	9.7	B8
Guinea pig	4	Unspecified	12.7	B9
Rabbit	4	Unspecified	11.0	B10

4 ACUTE DERMAL TOXICITY (Study Nos. C1 and C2)

4.1 Summary

Two studies indicate that TDI has very low acute dermal toxicity in the rabbit.

4.2 Study Assessments

The acute dermal toxicity of TDI has been evaluated in 2 studies on the rabbit. In Study C1, dermal applications of 2,4- TDI up to 16,000 mg/kg failed to produce organ damage or cause mortality, although there was severe local skin irritation. In Study C2, TDI (unspecified form) was applied to intact or abraded skin at doses up to 9.4g/kg and observations undertaken over 14 days. Moderate - marked skin irritation occurred but there was no indication of a systemic effect and no mortality. The acute dermal LD_{50} was therefore >9.4g/kg.

5 SKIN IRRITATION (Study Nos. D1 and D2)

5.1 Summary

On the basis of two rabbit studies, TDI would appear to be a moderate - marked skin irritant.

5.2 Study Assessments

Skin irritation was assessed in two rabbit studies. In Study D1, 2,4-TDI was applied to intact or abraded skin and occluded for 24h. There was some variation in the results from individual rabbits but overall the reaction was of moderate irritation, the effects of which resolved within 3 weeks. In Study D2, TDI (unspecified form) was applied at doses up to 9.4g/kg and occluded for 24h. Skin irritation increased to a maximum after 5-10 days with marked erythema, oedema, atonia and coriaceousness. Recovery occurred within 14 days.

6 EYE IRRITATION (Study Nos E1-E3)

6.1 Summary

The overall evaluation of TDI (either as 2,4- isomer or mixed isomers) is that it is a moderate - severe eye irritant in the rabbit.

6.2 Study Assessments

TDI has been assessed for eye irritation in the rabbit. In Studies E1 and E2, similar procedures were used with 0.1 ml TDI placed in one eye of each rabbit, the other eye was used as control. The eyes were observed at intervals for a period of several days. In both studies, moderate - severe conjunctival irritation was seen within 24h. This persisted for up to 10 days. The cornea and iris were also affected. In the third study, only minimal details were given, (Study E3), but application of 2,4-TDI resulted in marked irritation of eyelids and mild damage to corneal epithelium.

7 SKIN SENSITISATION (Study Nos F1-F12)

7.1 Summary

The skin sensitisation potential of TDI has been thoroughly tested in a variety of studies in 3 species. In all cases and with all forms of TDI, i.e. single or mixed isomers, a significant and usually strong sensitisation effect was shown.

The 12 studies reported for skin sensitisation encompass guinea pig, mouse and rat testing to various protocols.

7.2 Study Assessments

7.2.1 Guinea pig studies

Study F1: 2,4-TDI, dissolved in n-butyl ether, was applied at a range of concentrations to the dorsum and then challenged with lower concentrations of TDI on new sites 5 days later. Dose dependent skin sensitisation was induced and a no-effect level was attained with induction of 4% TDI and challenge with 0.012% solution.

Studies F2 and F3: were undertaken to the same protocol for 2,4- and 2,6- TDI. 0.1 ml of 1% TDI solution in dinonyl phthalate was applied daily to the outer ear for 3 days and then challenged with 0.2 ml solution on the 7th day. Similar results were obtained for both isomers which were considered to be skin sensitisers.

In Study F4: 2,4- TDI was assessed by the Magnusson and Kligman procedure. It was administered by intradermal and dorsal application, and finally to the flank with a 1 week rest period between each application. The skin was assessed 24 and 48h afterwards. The compound was shown to be a medium-strong skin sensitiser in this test. Cross sensitisation was shown with MDI.

Study F5: TDI (80:20 isomer ratio) was applied as a 10% solution in olive oil to the dorsal area and then challenged with a 0.1% solution 7 days later on the flank. Contact sensitivity at maximum severity was observed in most of the animals.

7.2.2 Mouse studies

Skin sensitisation was assessed in several mouse studies by the ear swelling test. In each case the study protocol was similar, with a TDI solution in an organic solvent applied to the animal's back, abdomen or tail and then challenged a few days later with the TDI solution applied to the ear. The ear swelling response was measured usually 24h or 48h later.

Study F6: mice showed a significant response with 80:20 isomer ratio TDI.

In Study F7, with 2,4- TDI, a strong response was obtained by induction with 1-5% TDI and challenge with 1% TDI but with little response with challenge by 0.1% TDI.

The response of hairy and nude mice was investigated in Study F8. A significant response was obtained with 2,4-TDI in hairy mice but none in nude mice. It was suggested therefore, that thymus-derived T-lymphocytes may have a role in contact sensitisation since nude mice do not have a thymus.

In Study F9, the development of the response with time was assessed over a 72h period using 2,4-TDI. The maximum effect was obtained after 24h with 100% increase in ear thickness.

A strong response was obtained in Study F10 when TDI was applied in Freund's adjuvant id followed by topical application to the stomach. After 4 daily treatments a challenge was made 7 days later with an application to the ear. Ear thickness, as measured 24 and 48 hours later, increased 142% on average.

Dose response relationships were investigated in Study F11 using sensitising doses of 0.7 - 28 mg/kg TDI (80:20 isomer ratio). The dose sensitising 50% of the mice was 5.3 mg/kg. Cross sensitisation was shown by challenge with other isocyanates such as MDI and HDI.

7.2.3 Rat study

The use of the rat for the ear swelling test was assessed in Study F12. Induction was obtained by application of TDI (80:20 isomer ratio) in ethyl acetate to the back or tail and then a challenge 7 days later by application to the ear. Ear swelling responses were obtained with all forms of induction and showed that the rat can be used as a model.

8 REPEATED DOSE TOXICITY (Study Nos G1-G35)

8.1 Oral Studies (Study Nos.G1-G4)

8.1.1 Summary

The results of a 90 day gavage study on rats showed effects at 120 mg/kg/day and above as depressed body weight gain and adverse lung histopathology. Mice were much less affected with only a small increase in mortality at these levels. No effect levels were established at 30 mg/kg/day in rats and 60 mg/kg/day in mice.

8.1.2 Study Assessments

Gavage studies, over 14 or 90 days, were undertaken in rats or mice as a prelude to long term investigations with TDI (80:20 isomer ratio).

The two 14-day studies (G1 and G2) were carried out at dose levels from 30-500 mg/kg.bwt/day with 5 males and 5 females per group. For both species, there was no effect on clinical condition and no dose related mortality. Bodyweight gain was depressed in male rats at 120 mg/kg/day and above and in females at 500 mg/kg/day. There were no compound related changes in tissues upon gross examination of rats or mice.

The 90-day studies (G3 and G4) were carried out at dose levels of 15-240 mg/kg.bwt/day with 10 males, 10 females per group. Rats were more affected than mice. Bodyweight was depressed by about 10% in male rats at 120 and 240 mg/kg/day and there was also a small number of mortalities and clinical effects in males at these dose levels. Mild-moderate mucoid bronchopneumonia was seen in male rats at 240 mg/kg./day and in a small number of females at this level. Less severe lesions occurred at lower incidence at 120 mg/kg/day. Apart from a low incidence of mortality at 120 and 240 mg/kg/day, mice were unaffected by

the administration of TDI.

8.2 Inhalation Studies (Study Nos.G5-G35)

8.2.1 Summary

In summary, the various inhalation studies on TDI have defined its main toxicological characteristics in several animal species. The main effect is upon the respiratory tract with severe toxic signs and increasing mortality at concentrations of about 1 ppm and above. Exposure concentrations of about 0.3-1 ppm produce a variety effects, mainly associated with the respiratory tract and some depression of bodyweight gain. Microscopic evidence of changes in respiratory tract tissues is seen at these levels. The more conventional 14-28 day rat studies indicate no-effect levels for these type of changes to be in the region of 0.1-0.2 ppm.

8.2.2 Study Assessments

Repeated dose inhalation toxicity has been studied using a variety of test protocols with a number of species. Rats, mice, hamsters, rabbits, guinea pigs and dogs have been investigated with exposure periods from a few days to a few months.

8.2.3 Rat studies

In Study G5, male rats were exposed to TDI (unspecified form) for 30min/day, 5 days/week for 2 weeks at concentrations of 0.34, 2.1 or 7.4 ppm. There was bodyweight gain depression and signs of ptyalism at 2.1 and 7.4 ppm. A NOEL of 0.34 ppm was established in this study.

TDI (80:20 isomer ratio) was applied in aerosol form in Study G6, for 4h/day for 5 days at 0.041 or 0.137 mg/litre (19ppm). All rats showed signs of toxic effect with reduced respiration and eye and nose irritation. There was high mortality at 0.137 mg/litre. In Study G7, the rats were exposed to two concentrations of the TDI aerosol (0.2 and 2 ppm) for 4h/day, 5 days/week for 4 weeks. Several effects occurred at 2 ppm including laboured breathing, depressed bodyweight gain and severe lung damage. There were no effects at 0.2ppm.

Study G8 was a very comprehensive investigation of TDI (80:20 isomer ratio) over a 3-week period. Rats were exposed to 0.24, 0.67 or 2.83 ppm for 6h/day, 5 days/week. A variety of effects occurred at 2.83 ppm and there were a few mortalities. Effects included decreased respiration rate, decreased urine volume, increased blood urea and red cell parameters, and histopathological changes to respiratory tract organs. Similar but less severe histopathological changes occurred at 0.67 ppm. Some effect was also seen at 0.24 ppm, but since atmospheric TDI levels were difficult to control at this level, the effects may have been due to high excursions of up to 0.6 ppm.

Studies G9 and G10, assessed the effect of TDI (80:20 isomer ratio) on 2 strains of rat, Fischer 344 and Sprague-Dawley. Rats were exposed for 6h/day, for 20-22 exposure days over a 30 day period at concentrations of 0.1 or 0.3 ppm. The comparison of the 2 strains was made difficult by a glandular infection in the Sprague-Dawley strain which complicated the interpretation of respiratory irritation seen in all animals including controls. However, only the 0.3 ppm group was considered to be affected by TDI exposure. Bodyweight gain was significantly decreased at 0.3 ppm in the Fischer rats and to a lesser extent at 0.1 ppm.

In Studies G13 and 14, rats were exposed to 0.1 ppm TDI (unspecified form) for varying time periods over several weeks. After exposure for 6h/day, 1 day/week for 38 weeks all animals showed pneumonitis to varying degree in the lungs. In a more intensive exposure regime of 6h/day, 5 days/week for a total of 58 exposures, rats were killed at successive times after the last exposure for an assessment of the development of airway lesions. Inflammation of the lungs was pronounced after 3 days, while after 20 days 5/6 rats showed purulent bronchiectasis with areas of bronchopneumonia and chronic tracheitis. It should be noted however, that control rats also showed findings similar to chronic murine pneumonia.

Studies G18, G19, and G20, were concerned with the effect of a high concentration of TDI, about 10 ppm, over short exposure periods of 2, 3 or 5 days. The two TDI isomers, either singly or as a 65:35 mixture, were administered for 6h/day. High mortalities occurred within each time period and all rats had died within 5 days. Death was due to blockage of respiratory passages with separated mucosa from bronchi and trachea.

Studies G21 and G22, were of a similar design to those just described, assessing the effect of lower concentrations of the 65:35 isomer mixture. At 4.5 ppm, 13/20 rats died within 4 days. At 0.95 ppm, 15/20 rats died within 12 days. Lungs from these animals showed severe peribronchitis and bronchopneumonia.

In more extended exposure regimes the effect of the 65:35 isomer mixture was assessed at lower concentrations over longer periods. In Study G23, the concentration was 0.48ppm and exposure for 6h/day, 6 days/week for 2 weeks, repeated after a 4-week break. Two groups were exposed, one of rats of initial bodyweight 90-124g and the other of bodyweight 140-184g. The younger animals were much more affected with 9/20 dying during the first 2-week exposure period. There were no mortalities in the older group. The lungs showed peribronchitis and bronchopneumonia after the exposure periods, the changes reversing to normal findings 8 weeks after the last exposure. In Study G24, the two exposure periods lasted for 4 weeks each and the TDI concentration was 0.11 ppm. No deaths occurred and, except for a small decrease in bodyweight, there were no other effects due to exposure.

In two brief reported Studies G27 and G28, rats were exposed to 2,4-TDI at concentrations between 1 and 2ppm for varying time periods of 10-79 days (6h/day). No observable effects were reported but there was microscopic evidence of bronchitis in the lungs.

8.2.4 Other species

In Study G11, mice were exposed to TDI (80:20 isomer ratio) at 0.1 or 0.3 ppm for 6h/day for 20-22 exposure days over a 30 day period. There were no effects on clinical condition, bodyweight, haematology, blood biochemistry, organ weight or gross pathology.

Mice were exposed to 0.4 ppm TDI (unspecified form) in Study G34. Exposure was for 6h/day for 5 days, followed by a 3-day recovery period. Lesions of the upper respiratory tract were produced, including inflammation, ulceration and squamous metaplasia. Only partial recovery occurred within 3 days. There was no effect on lungs or trachea.

In Study G35, mice were exposed to a number of concentrations of 2,4-TDI for evaluation of respiratory rate effects. Exposures for 3h/day for 5 days at and above 0.023 ppm produced a cumulative decrease in respiratory rate. A concentration of 0.018 ppm was without effect. Two separate groups, exposed to 0.031 or 0.25 ppm were assessed for changes in the nasal area. The higher level produced microscopic changes in the nasal mucosa and epithelium, while no effect was seen at 0.031 ppm.

In Study G17, Guinea pigs were exposed to TDI (unspecified form) for 6h/day, 5 days/week for 58 exposures over 78 days at a concentration of 0.1 ppm. During the first 30-90 min of each exposure all animals showed general discomfort and hyperactivity which decreased before exposure ended; 4/9 animals died during the study. Microscopic examination of the lungs showed inflammation, varying from slight diffuse to prominent pneumonitis.

In Studies G25 and G26 guinea pigs were exposed to 0.49 ppm TDI (65:35 isomer ratio) for 6h/day, 5 days/week for 2 weeks, repeated after a 4-week break or to 0.11 ppm for 6h/day, 5 days/week for 4 weeks, repeated after a 4-week interval. At the higher exposure level 2/5 animals died within 11 days of the 1st exposure period. At 0.11 ppm there were no deaths; bodyweight was depressed at both exposure periods.

In a briefly reported Study G30, guinea pigs were exposed to 2,4-TDI at 1.5 ppm for 6h/day for periods of 23-78 days. All animals showed bronchitis and varying degrees of bronchial pneumonia.

Detailed investigations of the respiratory tract were undertaken in guinea pigs exposed to 2,4-TDI in Studies G32 and G33. In the shorter exposure study, animals were exposed for 4h/day for 5 days to 3.1 ppm TDI and then killed at varying times after the last exposure. There was marked damaged to the airways epithelium during the 1st week after exposure with almost compete recovery by 3 weeks. In the longer study over 14 days at 0.03 or 0.26 ppm there was a pattern of infolding of the surface of the epithelium, more apparent than in controls, at both levels. No inflammation was apparent.

In Study G12, hamsters were exposed to TDI (80:20 isomer ratio) at 0.1 and 0.3 ppm for 6h/day for 20-22 exposure days for a 30 days period. There were no mortalities or effects on clinical condition, bodyweight, haematology, blood biochemistry or organ weights. Microscopic changes were detected in animals at 0.3 ppm with an increased incidence of focal hyperplasia of the respiratory epithelium of the nasal turbinates.

Rabbits were exposed to 0.1 ppm TDI (unspecified form) for extended time periods in Studies G15 and 16. After 6h exposures, 1 day/week, for 38 weeks the animals showed spastic-like breathing and limb movement. During each daily exposure, they showed general discomfort and hyperactivity which decreased with time. Tissues were examined after 58 exposures in the other study at 6h/day, 5 days/week. Three days after the last exposure, lungs showed areas of bronchopneumonia. After 10 days there was extensive inflammatory involvement and, after 20 days, chronic bronchitis was the only major abnormality.

In briefly reported Studies G29 and G31, rabbits or dogs were exposed to 1.5 ppm 2,4-TDI for various time periods. Two rabbits died after 5x6h exposures and the remaining 3 were killed after 19, 52 and 7 exposures. All showed bronchitis. The dogs showed signs of lachrymation, coughing and restlessness during exposure. At termination there was mild congestion and inflammation of the trachea and large bronchi.

8.2.5 Discussion on repeated dose inhalation toxicity

It is difficult to adequately summarise the numerous studies on repeated exposure inhalation toxicity because of the variation in protocols, reporting standards and study objectives. Only 4 of the rat studies, for example, conform to standard type 14-28 day test protocols (G7-G10). No 90-day studies have been reported. Unfortunately even with the more standardised studies some event has complicated the interpretation of results. In Study G8, the concentration at the lowest exposure level was variable and a no effect level could not be established over the 21-day period. Glandular infection compromised the evaluation of effects in Sprague-Dawley rats in Study G10.

Some of the rat studies were also probably affected by secondary infection of the respiratory tract. This complication may have exaggerated the findings in Studies G13 and G14 and G18-G24.

Despite the difficulties described above some attempt can be made to compare the findings of the different studies to discern the toxic action of TDI at varying exposure concentrations and time periods. Taking the more standard rat studies G7-G10 as the basis for evaluation it is seen that an exposure level of 2,8 ppm over 21 days causes some mortality and a variety of effects associated with the respiratory tract (Study G8). These include laboured breathing, decreased respiration rate, increased airway resistance and histopathological changes in the nasal passages, larynx, trachea and lung. A similar outcome was obtained for 2 ppm over 28 days (Study G7). Similar, but less effect was obtained at 0.67 ppm (no mortality) over 21 days (Study G8). At an exposure level of 0.3 ppm over 30 days the most consistent effect on two strains of rat was reduced bodyweight gain (Studies G9 and G10). No effects were seen at 0.2 ppm in Study G7 and very minor bodyweight gain depression at 0.1 ppm in Study G9. The overall no effect level for repeated inhalation exposure in the rat would therefore appear to be in the region of 0.1-0.2 ppm.

The outcome of the rat studies is summarised in table 8.1 and shows a reasonable gradation of effect with exposure period and concentration as indicated with the standard studies just described.

Some workers compared the effects of TDI on rat and other species and the reports of these studies provide insights into any possible species differences. Thus the rat, mouse and hamster were exposed to TDI at 0.1 and 0.3 ppm over 30 days in studies G9-G12. These evaluations showed the mouse to be somewhat less affected than rat or hamster, i.e.no effect on mouse at 0.3 ppm. In another series of comparative studies at 0.1 ppm (Study Nos.G13-G17) similar effects occurred in rats, rabbits and guinea pigs. Comparatively similar responses were also obtained for rats and guinea pigs at 0.11 and 0.49 ppm in studies G23-G26. On the evidence of these studies there appears to be little difference between common laboratory species in their reaction to the repeated exposure to TDI. It should be noted however, that in a study assessing the effect on respiratory rate, effects were seen at levels as low as 0.023 ppm in the mouse (Study G35).

Table 8.1 Toxic effect of TDI in the rat by repeated inhalation exposure.

TDI Form	Atmospheric Concentration (ppm)	Exposure period (days)	Main Effect	Study No.
80 : 20	19	5	lethal	G6
2,4- or 2,6- or 65 : 35	10	2-5	lethal	G18-G20
80 : 20	5.7	5	low mortality respiratory tract irritation	G6
65 : 35	4.5	4	high mortality	G21
80 : 20	2.8	21	low mortality respiratory tract effects	G8
80 : 20	2	28	low mortality respiratory tract effects	G7
65 : 35	0.95	12	high mortality	G22
80 : 20	0.67	21	respiratory tract effects	G8
80 : 20	0.3	30	reduced bodyweight gain	G9
80 : 20	0.2	28	no effect	G7
65 : 35	0.11	2x28	reduced bodyweight gain	G24
80 : 20	0.1	30	slightly reduced bodyweight gain	G9
80 : 20	0.1	30	no effect	G10

9 GENETIC TOXICITY IN VITRO (Study Nos H1-H20)

9.1 Summary

A wide variety of results was obtained with the range of in vitro assays on TDI. The most consistent result was with the bacterial mutation assay using tester strains TA 98 & TA 100 in the presence of metabolic activation. These showed positive results for all forms of TDI in several tests. Negative results were obtained in the absence of S9 and, usually, other strains such as TA 1535 & TA 1537 did not respond either in the presence or absence of S9. The results of cytogenetic and SCE tests were inconsistent; negative or ambiguous results outweighing two positive results in the absence of metabolic activation. Mammalian cell transformation assays were negative.

In assessing the results of these studies, a complicating factor of solvent interaction must be taken into account. DMSO was the solvent for most of the above studies and it has been shown that 2,4-TDI hydrolyses in this solvent in the presence of moisture to give significant quantities of other products. There is, therefore, some doubt if the results of the in vitro tests reflect the action of TDI or of its hydrolysis products (Gahlmann et al 1993).

Thus, although it could be concluded that TDI is a bacterial mutagen on the evidence of Ames tests, a final assessment has to be deferred until the question of the influence of TDI solvent interaction products is clarified.

9.2 Study Assessments

9.2.1 Bacterial Mutation Assays (Study Nos H1-H10)

Ames tests, with all forms of TDI, have produced a variety of results with the different Salmonella tester strains.

Two investigations with 2,4-TDI, Study Nos H1 and H10, gave negative results for all tester strains; however, experimental details are minimal so it is difficult to judge the reliability of the test procedures.

In a series of tests (Studies H2-H7), 2,4-, 2,6- or the 80:20 isomer mixture of TDI were each incubated with TA97, TA98, TA100 and TA1535 tester strains, with or without S9. For each form of TDI, positive results were obtained with TA98 and TA100 in the presence of S9. Positive results for these two tester strains in the presence of S9 were also obtained in Study H9 for the 80:20 isomer mixture.

9.2.2 Chromosomal Assays (Study Nos. H11-H18)

The assays comprised cytogenetic and sister chromatic exchange tests in a variety of test systems.

In Studies H11 and H12, the tests were carried out with male human whole blood lymphocyte culture, with and without S9. Slight, non-dose related increases in chromosome aberrations were obtained in the cytogenetic assay but the SCE test was negative.

In a series of studies (Nos.H13-H18), the different forms of TDI (2,4-, 2,6- or the 80:20 isomer mixture) were each incubated with Chinese hamster ovary cells. The results were not consistent, with 2,4-TDI and the 80:20 mixture negative in the cytogenetic assay while 2,6-TDI was positive in the absence of S9. In the SCE assays, 2,4- & 2,6-TDI gave ambiguous findings while the 80:20 mixture was positive in the absence of S9.

9.2.3 Cell Transformation Assays

Studies H19 & H20 were concerned with mammalian cell transformation tests using either Syrian hamster kidney BHK-21 C13 cells or human lung W1-38 cell cultures. In both cases, 2,4-TDI was negative in the presence or absence of S9.

Reference:

Gahlmann R, Herbold B, Ruckes A, & Seel K, Untersuchungen zur stabilitat aromatischer diisocyanate in dimethyl sulfoxide (DMSO): Toluylendiisocyanate (TDI) und diphenylmethandiisocyanate (MDI) in Ames-Test, Zbl Arbeitsmed 43: 34-38.

10 GENETIC TOXICITY IN VIVO (Study Nos J1 - J5)

10.1 Summary

Tests using exposure of TDI by inhalation indicate that the compound is unlikely to be mutagenic in the intact mammalian system.

10.2 Study Assessments

Micronucleus assays and an unscheduled DNA synthesis test have been undertaken on the 80:20 isomer mixture.

Study J1 was a preliminary test at high exposure levels. Male and female mice were exposed to concentrations of 7.5 - 18.9 ppm TDI for 6h and bone marrows sampled 24, 48 & 72h afterwards. Small, statistically signification increases in micronucleated polychromatic erythrocytes(MPE) were obtained. This was assessed further in Study J2 at lower exposure levels of 3.7 -7.5 ppm. Small, statistically significant increases in MPE were seen in females only, but these results were within control range and not considered to be biologically significant.

Mutagenic activity was evaluated in micronucleus assays in the mouse and rat after inhalation exposure to TDI over a period of 4 weeks in Studies J3 & J4. The animals were exposed to concentrations of 0.05 and 0.15 ppm. There were no treatment related increases in the number of MPE from bone marrow preparation from the mice. In rats, a small but significant increase in MPE occurred only at the lower exposure level and was therefore not considered to be biologically significant.

In the UDS assay, Study J5, rats were exposed, by inhalation, to 0.077, 0.4 or 1.49 ppm TDI for 4h. The compound did not induce unscheduled DNA synthesis in lung or hepatocytes at any of the exposure levels.

11 CARCINOGENICITY (Study Nos. K1 - K4)

The carcinogenic potential of TDI (80:20 isomer ratio) has been evaluated in long term, oral and inhalation studies in rats and mice.

11.1 Oral Studies (Study No.s K1 & K2)

11.1.2 Summary

Two oral studies in rats and mice at high dose levels showed a greatly increased mortality which indicated that the doses were far too high for an appropriate chronic toxicity and carcinogenicity evaluation. The rats also showed a very high incidence of acute bronchopneumonia, further indicating the extremely high level of toxicity throughout the studies. Analysis of the TDI dosing solutions showed that the concentration of the test substance was significantly below the target values, up to 23% below in some cases, due to interaction between TDI and the corn oil producing other products. There must therefore be some doubt whether TDI alone was responsible for the increased tumour incidences recorded in treated animals. Because of these complicating factors and possible deficiencies in study execution (Ader et al 1987), it is difficult to assess the relevance of these two studies as evaluations of TDI carcinogenicity.

Reference: Ader A W, Carney I F & Loeser E. Risk evaluation of chronic exposure to TDI based on long-term animal studies. Proc. SPI/FSK Polyurethanes World Congress 1987, 188-192.

11.1.3 Study Assessments

TDI, dissolved in corn oil, was administered by gavage in long term rat and mouse studies undertaken in the National Toxicology Program (NTP) of the US Department of Health & Human Services.

In the rat study (Study K1), groups of 50 males, 50 females were given nominal doses of TDI of 30 and 60 mg/kg in males and 60 and 120 mg/kg in females. Dosing was 5 day/week for 106 weeks. Analysis showed that target doses were not attained because of interaction of TDI with water in the corn oil. Although no clinical signs were seen, there was a dose-related depression in bodyweight gain, greater than 10%, in all groups. Mortality was much greater in treated groups than in controls, e.g. 14/50, 32/50, 40/50 in male groups at 104 weeks. Acute bronchopneumonia was also found at increased incidence in dosed males and females, and was 50% in females at 120 mg/kg compared with 2% in controls.

Tumour incidence had to be adjusted in treated groups, compared to controls, because of high mortality. Statistical analyses, taking account of this, showed increases for subcutaneous tissue and pancreatic cell tumours in treated males and females and for mammary gland and liver adenomas in treated females. About 50% of these tumours were found in rats at termination, the remainder in animals dying between weeks 77 and 108.

In the mouse study (Study K2), undertaken to a similar protocol, the dose levels were 120 or 240 mg/kg in males and 60 or 120 mg/kg in females (nominal values). There were no clinical signs of toxicity and females showed a slight depression of bodyweight gain at the top dose only. Males showed a dose related depression of bodyweight gain in treated groups. Again, as for the rat study, there was an increased mortality in treated groups, particularly in males, compared to controls. Male treated groups also showed a very high incidence of kidney cytomegaly. After adjusting for differential mortality between groups and using appropriate statistical analysis, increased tumour incidence due to treatment was considered to occur in female mice with hepatocellular adenomas at the top dose of 120 mg/kg. A slight increase in circulatory system tumours was also indicated at this dose.

11.2 Inhalation studies (Study Nos. K3 and K4)

11.2.1 Summary

The two inhalation studies in rats and mice showed a variety of effects, particularly at the top exposure level, which included reduced bodyweight gain and microscopic changes in the nasal cavity and, in mice, in the lower respiratory tract. In each case, however, there was no indication of a carcinogenic effect.

11.2.2 Study Assessments

Groups of male and female rats and mice were exposed to atmospheric concentrations of 0.05 or 0.15 ppm TDI over a 2 year period.

In Study K3, there were no treatment related effects on mortality or for toxic signs in rats. Bodyweight gain was reduced in both sexes at the top exposure level and there was an increased incidence of rhinitis in the nasal cavity at both exposure levels in females and in the top level males. There was no evidence for any treatment related increase in tumour incidences.

A similar profile of results was obtained for mice in Study K4. Mortality was somewhat increased in TDI exposed female mice and there were increased signs of swollen abdomens and opaque watery eyes, which may have been treatment related, from week 65 onwards. Bodyweight gain was reduced in both sexes at the top exposure level. Microscopic examination showed increased incidence and severity of chronic rhinitis with exposure level and also an effect in the lower respiratory tract of interstitial pneumonitis, catarrhal bronchitis and bronchiolitis. However, there was no evidence for any treatment related increase in tumour incidence.

11.3 Overall evaluation of carcinogenicity of TDI

The evaluation by 2 routes of administration has shown different results by the oral gavage or inhalation procedures in both rats and mice. Although the oral studies evaluation is complicated by very high dose and procedural difficulties, it is apparent that some carcinogenic activity results from this route of administration. In contrast, the inhalation study route shows no indication of carcinogenic activity.

Apart from the obvious difference in TDI loading in the two sets of studies, differences in metabolism of TDI via the two routes may also be a reason for the differing outcome. As shown in Section 13 on Pharmacokinetics and metabolism, 2,4-TDI gives rise to significant quantities of 2,4 diaminotoluene (2,4-TDA) following oral dosing, due to hydrolysis. TDA has been shown to give rise to hepatocellular tumours in rats and mice in long term oral studies and also mammary gland adenomas in female rats and subcutaneous fibromas in males. That is, a similar spectrum of tumours as produced in the TDI oral studies. Following inhalation exposure to 14 C-TDI, the excretion and distribution of radiolabelled products are different from those of oral dosing. The proportion of free or acetylated TDA is much lower after inhalation. Other studies have shown that the proportion of products conjugated with high molecular weight protein is much greater after inhalation exposure than with oral dosing. This indicates less availability for TDI to form TDA after inhalation.

The above information emphasises and supports the lack of carcinogenic action shown by TDI after inhalation exposure to rats and mice. It should also be noted that TDI is not mutagenic in rats or mice, in vivo, following inhalation administration (Study No.s J1-J5). For the purposes of risk evaluation in humans, the results of the long term inhalation studies give the most relevant information on which to base carcinogenic assessments.

12 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY (Study Nos. L1 & L2)

12.1 Summary

TDI has been tested for reproductive toxicity in a 2-generation rat study at exposure levels up to 0.3 ppm and in a developmental toxicity - teratogenicity rat study at levels up to 0.5 ppm. Although adult toxicity was established at the highest exposure levels in both studies there was no indication that TDI caused reproductive, developmental or teratogenic effects at the levels tested.

12.2 Study Assessments

TDI (80:20 isomer ratio) has been the subject of a two-generation rat reproduction study and a rat developmental toxicity - teratogenicity assessment.

12.2.1 Two-generation rat study (Study No. L1)

The reproduction toxicity potential of TDI in the rat was assessed in a standard 2-generation study with inhalation exposure. Groups of males and females were exposed to 0, 0.02, 0.08 or 0.30 ppm TDI for a 10 week pre-mating period and during mating. Parents for the second generation were selected from the litters at day 21 and exposed similarly for pre-mating and subsequent periods.

Toxic effects were shown for parents of both generations at 0.3 ppm, primarily as microscopic changes in the nasal region. Rhinitis occurred at increased incidence in males and females also at 0.08 ppm in the F1 generation and males were affected at 0.02 ppm. Pup bodyweight was reduced up to day 21 day in the second generation at 0.08 and 0.3 ppm. There were no effects however on the range of reproductive indices examined in both generations.

12.2.2 Developmental toxicity - teratogenicity (Study No. L2)

Pregnant rats were exposed to TDI vapour over days 6-15 of gestation. The exposure levels were 0, 0.02, 0.10 and 0.50 ppm TDI. Toxic effects occurred in the dams at 0.5 ppm as respiratory noise and reduced bodyweight gain. There was no effect, however, on pregnancy rate, number of corpora lutea, viable implants, or live foetuses, nor was there any indication of increased incidence of external, visceral or skeletal malformations in the offspring. An increased incidence of poorly ossified cervical centrum 5 at 0.5 ppm indicated minimal foetotoxicity. The NOEL for maternal and foetotoxicity was therefore 0.1 ppm, but TDI was not teratogenic at the exposure levels up to and including 0.5 ppm.

13 PHARMACOKINETICS AND METABOLISM (Study Nos. M1-M13)

13.1 Summary

The main features of the uptake, excretion and distribution of TDI, in its various forms, have been characterised in several studies. Absorption is low after gavage dosing with the majority of the dose excreted in the faeces within a few days. Faecal excretion was also high after inhalation exposure. Tissue retention was generally low, although a higher percentage of the dose was present after inhalation than after oral administration. After inhalation, the highest tissue concentrations were in the respiratory tract; elimination was biphasic with a slow second phase. The majority of blood radioactivity appeared to be in the plasma after ^{14}C-TDI administration, much of this associated with a protein conjugate >70k Da.

Metabolic investigation showed that acid-labile conjugates were present in urine after both oral or inhalation exposure, although the proportion was significantly greater from the latter. Also, free TDA was present after oral, but not after inhalation administration. In the case of 2,6-TDI, a major urinary metabolite was 2,6-bis (acetylamino) toluene at low doses. This could have been formed after acetylation of the absorbed hydrolysis products of 2,6-TDI.

13.2 Study Assessments

Several studies have been undertaken investigating the fate of TDI in rats and guinea pigs by oral or inhalation routes of administration.

Study Nos. M1 & M2 were the earliest investigations to examine the uptake, distribution and excretion of TDI (mixed Isomers 84:16). In the preliminary study (M1), ^{14}C-TDI was injected i.m. into rats and the blood sampled at regular intervals thereafter. Urine, faeces and expired CO_2 were also collected and all samples measured for radioactivity. Blood activity peaked within 24 h; the $T_{\frac{1}{2}}$ for diffusion from the muscle was about 30 min. Fifty three per cent of the dose was excreted in urine after 360 h together with 39% in faeces. In the following inhalation study (M2), elimination of ^{14}C from blood was biphasic. It was shown that 90% of radioactivity in the plasma was associated with proteins. Eighty six per cent of the dose was eliminated in 5 days with faecal excretion greater than urinary excretion. Further detailed information could not be ascertained since a full report on the study is not available.

Study Nos. M3 & M4 examined the fate of ^{14}C-TDI (80:20 isomer ratio) after single oral or inhalation exposure to rats. After a gavage dose (6 or 60 mg/kg), radioactivity appeared in blood within 30 min, peaked at 1-2 h, then decreased slowly. Most of the activity, equivalent to 76-81% of the dose was excreted in faeces, mainly within 6-48h. 23% was excreted in urine (low dose) and 16% at the high dose. After a 4 h exposure at 0.6 or 2 ppm TDI, radioactivity was present in blood, equivalent to 4% of dose at the higher exposure level and 2% at the lower level. Faecal excretion, over 96 h, at 53-54% was again higher than urinary excretion (24% for low exposure, 20% for high). Tissue activity was low after either oral or inhalation administration. In both cases, the metabolic profile in urine and faeces was complex and no attempt was made to identify individual components.

Further comparisons between the outcome of gavage dosing at 60 mg/kg and 4 h inhalation exposure at 2 ppm TDI were examined in Study M9. Blood was sampled 2 h after the gavage dose or immediately after exposure, and the plasma separated and examined by molecular sieve fractionation and gel electrophoresis. The majority of the radioactivity in the plasma, in each case, was in a conjugated form. The predominant conjugate after inhalation had a relative molecular weight of 70k DA. Less was found after oral dosing when more low molecular weight conjugates were present.

The uptake and distribution of 2,4-TDI was investigated in guinea pigs in Study M10. The animals were exposed to a range of ^{14}C-TDI vapour concentrations for periods of 1-5 h. During exposure, the rate of uptake into the blood was linear for air concentrations ranging from 0.00005 - 0.146 ppm TDI. The uptake continued to increase for about 24h post-exposure followed by a slow decline. Tissues showing the highest levels of activity were the trachea and lungs, with residual activity persisting for up to 2 weeks.

A similar investigation was conducted in rats in Study M11 and the results compared with those from guinea pigs in study M10 above. The rats were exposed to ^{14}C-TDI at air concentrations of 0.026-0.82 ppm for 4h, and blood and a range of tissues collected immediately after exposure. Plasma was separated from blood for molecular sieve fractionation and gel electrophoresis. The uptake of ^{14}C into the bloodstream was similar to that for guinea pigs and, in both species, the majority of the activity was in the plasma. The predominant form of radioactivity in plasma, in both species, was associated with conjugated protein >70k Da. The distribution of activity was similar in the tissues of both species with the highest levels in the airways.

In two brief reports, M12 and M13, inhalation exposure of guinea pigs to 1 ppm TDI for 3h/day for 5 days and subsequent reaction after challenge with 0.1 ppm ^{14}C-TDI was described. Radioactivity appeared in the bloodstream of sensitised animals 5 times faster than in challenged controls. The activity was mainly in the plasma and associated with the 77k Da protein in TDI exposed animals. Autoradiography showed that the ^{14}C- label penetrated as far as the terminal bronchioles.

13.3 Discussion

Differences between the metabolism of 2,4-TDI by the oral and inhalation routes may help explain differences in toxicity, particularly carcinogenicity (see section 11). In particular, the presence of free TDA after oral dosing of TDI to rats is of interest. 2,4-TDA has been shown to be a carcinogen in rodents, producing a range of tumours similar to those found after long term oral administration of TDI. Other differences, such as the greater proportion of acid labile urinary conjugates after TDI inhalation and greater amount of plasma high molecular weight protein conjugate, may also help to explain the differences in toxic action between the two routes.

The rate of uptake of ^{14}C-TDI into the blood during inhalation exposure, the preponderance of activity in the plasma, the association of this activity with a high molecular weight protein and the ^{14}C-tissue distribution, was the same in rats and guinea pigs.

14 IMMUNOTOXICITY (Study Nos. N1 - N6)

14.1 Summary

Several attempts have been made to develop an animal model for studying the induction of pulmonary hypersensitivity to airborne TDI. Although some success has been obtained, following topical or inhalation administration, the results are not always reproducible and may depend upon the nature of the hapten- protein conjugate used for antibody assay or bronchial provocation.

14.2 Study Assessments

These studies were concerned with identifying the pulmonary hypersensitivity characteristics of TDI (as seen in humans) in animal models.

In Study N1, female guinea pigs were exposed to TDI (80:20 isomer ratio) vapour (0.25 ppm) 3h/day for 5 days. Respiratory rate decreased during exposures and TDI-specific antibodies were found in 6/16 animals. When animals were re-exposed to 0.02 ppm TDI for 30 min there was only a small decrease in respiratory rate, indicating that this regime did not elicit pulmonary hypersensitivity.

The topical route was used for the sensitising step in Study N2. Guinea pigs were given various dermal doses of TDI and were challenged 2 weeks later by exposure to 0.005 ppm TDI. A small proportion of the animals (25%) responded with increases in respiratory rate, indicating that skin contact can elicit pulmonary hypersensitivity.

In another evaluation, Study N3, groups of guinea pigs were exposed to TDI vapour for 3h/day for 5 days at concentrations of 0.12-10 ppm. On day 22, no TDI-antibodies were detected in serum of animals exposed to 0.12 ppm TDI but increasing titres were found at concentrations up to 0.93 ppm TDI. Bronchial provocation with antigen conjugates showed pulmonary hypersensitivity at 0.36-0.93 ppm TDI but not at higher concentrations. Exposure of another group of guinea pigs to 0.02 ppm TDI for 4 months did not result in production of TDI-specific antibodies nor, on bronchial provocation challenge, pulmonary hypersensitivity.

Study N4 was a further investigation of the pulmonary hypersensitivity model examined in the previous study. Guinea pigs were exposed to 0, 1, 3 or 4 ppm TDI vapour for 3h/day for 5 days and then challenged 22-30 days later with atmospheres of protein conjugates. It was shown that the animals reacted (increased respiratory rate) to one type of conjugate (the Karol conjugate) but not to another (the ICI conjugate). It was shown that both the antibody and pulmonary responses seen with TDI were dependent upon the quality of the hapten-protein conjugate used and it was concluded that further investigation of this animal model was required.

Study Nos.N5 and N6 were briefly reported investigations on guinea pigs and monkeys. Guinea pigs were exposed to 0.01-5 ppm TDI for 3 x 6h and then re-exposed 3 weeks later to 0.02 ppm TDI. Those animals previously exposed to high concentrations of TDI (2-5 ppm) showed reduced respiratory rate when re-exposed. Monkeys exposed to 0.13-0.7 ppm TDI for 6h exposures and then re-exposed 3 weeks later to 0.02 ppm or chronically exposed to 0.02 ppm TDI for a period of 23 x 6 h, showed no change in respiratory pattern.

15 BIOCHEMICAL OR CELLULAR INTERACTIONS (Study Nos. P1-P5)

15.1 Summary

In vitro tests indicate that the TDI isomers are capable of inhibiting cholinesterase activity obtained from various sources. The 2,6-isomer appears to be the more potent in this respect. TDI inhibits bronchial tree AChE activity after repeated exposure to rats indicating a localised effect. A study has shown that TDI is capable of a direct effect on airway smooth muscle.

15.2 Study Assessments

Most of the studies reviewed here are concerned with the effect of TDI on cholinesterase.

Studies P1 & P2 investigated the degree of acetyl cholinesterase inhibition by TDI (mixed isomers) in human erythrocytes in vitro and showed that the compound was a strong inhibitor under the conditions of assay. The effect was not quickly reversible.

The in vitro action of TDI on cholinesterase activity was studied in more detail in Study P3. The action of 2,4- and 2,6-TDI was compared in a series of investigations in human or horse serum, human plasma and eel ChE. 2,6-TDI was the more potent of the 2 isomers for human serum and eel ChE. When exposed at 1 ppm in air, the 2 isomers had similar inhibitory effect on horse serum ChE activity.

In vivo, Study P4, TDI (80:20 isomer ratio) was exposed to rats at several concentrations in a series of 4h exposures over 1-14 days. Acetycholinesterase activity was mea ured in blood and bronchial tree after the last exposure in each study. Blood AChE activity was not affected after single exposures up to 4.3 ppm TDI or 14 daily exposures of 1.2 ppm TDI. Some inhibition of bronchial tree AChE activity occurred after repeated exposure. In another trial, bronchial tree AChE activity was inhibited by 36% following exposure of rats to 1 ppm TDI, 5 days/week for 3 weeks.

In Study P5, tracheal strips from guinea pigs repeatedly exposed to 29 ppb 2,4-TDI were more responsive to contraction induced by carbachol, than controls.

Intratracheal administration at 0.3 ml TDI per guinea pig, (Study P6), resulted in coagulation of protein in the respiratory tract, leading to death from respiratory distress.

REVIEW OF TDI TOXICITY STUDIES

APPENDIX

SECTION

A	ACUTE ORAL TOXICITY
B	ACUTE INHALATION TOXICITY
C	ACUTE DERMAL TOXICITY
D	SKIN IRRITATION
E	EYE IRRITATION
F	SKIN SENSITISATION
G	REPEATED DOSE TOXICITY
H	GENETIC TOXICITY IN VITRO
J	GENETIC TOXICITY IN VIVO
K	CARCINOGENICITY
L	REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
M	PHARMACOKINETICS AND METABOLISM
N	IMMUNOTOXICITY
P	BIOCHEMICAL OR CELLULAR INTERACTIONS

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NOTES ON APPENDICES

1. The Appendices are presented in HEDSET format as required for the European Community electronic presentation of data on existing chemicals.

2. The HEDSET section 5 is concerned with TOXICITY, hence all the Appendices are numbered as sub-sections of 5.

3. The HEDSET format is very prescribed to allow computer searching by the European Community authorities. It requires:

   a) methods other than EC/OECD test methods to be referred to as "OTHER".

   b) test substances not stated in the HEDSET Section 1.1.-1.4 to be referred to as "OTHER". It is intended that the TDI HEDSET will be based on 80/20 TDI. It follows that tests on single isomers, for example, are listed as "OTHER". In these cases, the actual test substance is cited in the paragraph headed TS.

   c) multiple remarks, references, etc. to have separate RM, RE, etc. headings.

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5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	Rat
Value:	5800 mg/kg
Method:	Other
Year:	1957
GLP:	No
Test Substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4 TDI (CAS No.584-84-9)

RM: TDI dosed undiluted by stomach tube to groups of 10 rats (sex unspecified) at 6 dose levels (not stated).

RM: Pathological examination showed corrosive action in stomach.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth.1957, 15, 324-330.

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	Rat
Value:	5840 mg/kg
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, isomer ratio not specified. Purity not stated.

RM: Description of methodology is minimal but on some points, e.g. number rats/group, number of doses, observation period and observations, the protocol follows OECD guideline 401.

RM: Male rats only were used, 166-395 g bodyweight.

RM: TDI administered as neat material at doses of 1000, 2150 5,000 or 10,000 mg/kg.

RM: Mortality was 3/5 at 5000 and at 10,000 kg/kg. All rats showed clinical signs at 2150 mg/kg and above; hypoactivity and salivation. White granular particles in stomach at necropsy at 5000 and 10,000 mg/kg.

RE: Wazeter, F.X. Toluene diisocyante (TDI) and polymethylene polyphenyl isocyanate (PAPI): Acute toxicity studies (LD50)in male albino rats. International Research and Development Corporation Report 100-012, March 12, 1964.

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	Rat
Value:	4130 mg/kg
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Description of methodology is minimal but on some points, e.g. number rats per group, number of doses, observation period and observations, the protocol follows OECD guideline 401.

RM: Male and female rats, 10 weeks old.

RM: TDI given by gavage in corn oil at 6 dose levels from 2150-14,700 mg/kg.

RM: Mortality from 2/5 males at 2150 mg/kg to 5/5 males or females at 14,700 mg/kg.
At 10,000 or 14,700 mg/kg death was preceded by laboured breathing, inactivity and diarrhea
Weight loss in male survivors, smaller loss in female. White crystals in stomach and dark red lungs at necropsy, dose related.

RM: LD50 of 5110 mg/kg in males, 4130 mg/kg in females.

RE: National Toxicology Program. Toxicology and Carcinogenesis studies of commercial grade 2,4(80%)- and 2,6(20%)-toluene diisocyanate (CAS No.26471-62-5) in F344/N rats and B6C3F1 mice (gavage studies). US Dept. of Health & Human Services, August, 1986.

RE: Woolrich, P.F. Toxicity, industrial hygiene and medical control of TDI, MDI and PMPPI. Am. Ind. Hyg. Assocn. J., 43, 89-97.

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	Mouse
Value:	4130 mg/kg
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Description of methodology minimal, but on some points, e.g. number of rats per group, number of doses, observation period and observations, the protocol follows OECD guidelines 401.

RM: Male and female mice, 10 weeks old.

RM: TDI given by gavage in corn oil at 6 dose levels from 2150-10,000 mg/kg.

RM: Mortality from 1/5 females at 4640 mg/kg to 5/5 males or females at 10,000 mg/kg.
White crystals in stomach at necropsy, dose related.

RM: LD50 of 4130 mg/kg in males, 5620 mg/kg in females.

RE: National Toxicology Program. Toxicology & Carcinogenesis studies of commercial grade 2,4(80%)- and 2,6(20%)-toluene diisocyanate (CAS No.26471-62-5) in F344/N rats and BC3F1 mice (gavage studies). US Dept. of Health & Human Services, August 1986.

RE: Woolrich, P.F. Toxicity industrial hygiene and medical control of TDI, MDI and PMPPI. Am. Ind. Hyg. Assocn. J., 43, 89-97.

5.1.2 Acute Inhalation Toxicity

Type:	Other (see RM)
Species:	Rat
Exposure time:	6 hours
Value:	
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: No method detail given. Described only as 'acute inhalation studies'.

RM: 600 ppm was lethal to rats, 60 ppm was not lethal.

RM: Rats which died showed acute pulmonary congestion and oedema.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assoc. Archives Ind.Hlth, 1957, 15, 324-330.

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Rat
Exposure time:	one hour
Value:	66 ppm
Method:	Other
Year:	1980
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI 80:20 isomer ratio.

RM: TDI generated as a vapour. Atmosphere sampled by absorption in ethyl alcohol followed by HPLC analysis.

RM: 4 male, 4 female rats per group exposed to 17.4, 25.1, 43.2, 83.9 or 267.1 ppm TDI in air. Rats 6-10 weeks old, 150-300 g body weight. Rats observed during exposure and then every 2 days for 14 days. Bodyweights measured before exposure and then every 2 days for 14 days. Gross examination on all rats.

RM: Exposure dependent mortality from 1/8 at 17.4 ppm to 7/8 at 267 ppm.
Signs of wheezing and gasping increasing in severity with increasing exposure concentration, from 17.4-267 ppm.
Survivors lost weight during 1st 4 days after exposure. Lungs enlarged, pale, inflated at all levels and also filled with fluid at 43.2 ppm and above.

RE: Horspool, G.M. Toluene diisocyanate: acute inhalation toxicity in the rat. ICI Central Toxicology Laboratory Report No.CTL/T/1097, 2 Feb 1980.

5.1.2 Acute Inhalation Toxicity

Type:	Other (see RM)
Species:	Rat
Exposure time:	8 hours
Value:	
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: TDI generated as a vapour. Atmosphere sampled by absorption in 0.5% DMAB in acetic acid followed by colorimetric analysis.

RM: Only male rats used, 205-299 g bodyweight. 10 rats at one air concentration of 0.25 ppm TDI. Rats observed during exposure and then daily for 14 days. Bodyweight measured at 0, 7, and 14 days. Gross examination on all rats at termination.

RM: No mortality and no effect on bodyweight nor on tissues at necropsy.
Slight - moderate erythema during exposure period.

RE: Wazeter, F.X. PAPI, MDI, TDI: Acute inhalation exposure in male albino rats. International Research & Development Corporation, Report No.203-006, Nov.28, 1964.

5.1.2 Acute Inhalation Toxicity

Type:	Other (see RM)
Species:	Rat
Exposure time:	6 hours
Value:	
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, mixed isomers (unspecified)

RM: Preliminary dose range-finding study.

RM: Rats exposed to TDI in vapour form at concentrations of <1 - 13.5 ppm. Six rats per group, sex unspecified.

RM: Atmosphere sampled by impinger followed by colorimetric analysis.

RM: 3/6 rats died at 4 and 13.5 ppm.
Ocular - nasal irritation and laboured breathing at 2 ppm and above.
Exposure dependent bodyweight loss, slight at <1 ppm.
Exposure dependent emphysema and haemorrhage of lungs, slight at 1 ppm.

RE: Wazeter, F.X. Toluene diisocyante (TDI) and polymethylene polyphenylisocyanate (PAPI). Six-hour acute inhalation toxicity study in rats. International Research & Development Corporation, Report No. 100-012, March 26, 1964.

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Rat
Exposure time:	One hour
Value:	0.61 mg/l
Method:	Other
Year:	1970
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Test substance (TS)

RM: Male rats, 20 per group, exposed to TDI aerosol at concentrations 0.093-2.58 mg/l. Daily observation for 14 days.

RM: Atmosphere sampled by impinger, followed by colorimetric analysis.

RM: Exposure dependent mortality from 0.173 mg/l. Clinical signs of laboured breathing and irritation of eyes and nose. Typical isocyanate lung changes at necropsy.

RE: Kimmerle, G. Desmodur T80 (Gemisch aus 2,4- und 2,6-toluylendiisocyanate im verhaltnis 80:20). Untersuchungen zum inhalationstoxizitat. Bayer, Institut fur Toxikologie, Wuppertal, 10 July 1970.

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Rat
Exposure time:	4 hours
Value:	0.11 mg/l
Method:	Other
Year:	1970
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Test substance (TS)

RM: Male rats, 20 per group, exposed to TDI aerosol at concentrations 0.034 - 0.715 mg/l. Daily observations for 14 days.

RM: Atmosphere sampled by impinger, followed by colorimetric analysis.

RM: Exposure dependent mortality from 0.057 mg/l. Clinical signs of laboured breathing and irritation of eyes and nose. Typical isocyanate lung changes at necropsy.

RE: Kimmerle, G. Desmodur T80 (Gemisch aus 2,4-und 2,6-toluylendiisocyanate im verhaltnis 80:20) Untersuchungen zum inhalationstoxiztat. Bayer, Institut fur Toxikologie, Wuppertal, 10 July 1970.

5.2.1 Skin Irritation

Species:	Rabbit
Result:	Irritating
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: TDI applied to intact or abraded skin of male or female rabbits (1 male, 1 female per group) at doses of 2500-9400 mg/kg. Occluded for 24 hours. Skin examined for irritation after washing and observed for 14 days.

RM: Skin irritation at each dose, initially slight, with peak effect at 5-10 days with moderate - marked erythema, oedema, atonia and coriaceousness. Recovery almost complete within 14 days. Moderate - marked desquamation observed at day 14. Fissuring peaked at moderate - marked days 10-12, then negative - slight at day 14.

RE: Wazeter, F.X. Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI). Acute dermal toxicity studies (LD50) in the albino rabbit. International Research & Development Corporation, Report No.100-012, January 27, 1964.

5.2.2 Eye Irritation

Species:	Rabbit
Result:	Highly irritating
Method:	Other
Year:	1976
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI, 97% purity (CAS No.584-84-9)

RM: 0.1 ml TDI in conjunctivae of left eye, right eye as control. Cornea, iris, conjunctivae observed at 24, 48, 72, 96 hours and 7 days. 6 females per group.

RM: Severe irritation of conjunctivae and cornea within 24 hours. Severe conjunctivitis in 2/6 rabbits at 6 days. Corneal lesions regressing at this time. Keratoconjunctivitis cleared in 3-4 weeks.

RM: TDI classed as a severe eye irritant on the Kay & Calandra scale.

RE: DuPrat, P., Gradiski, D. and Marignac, B. Pouvoir irritant et allergisant de deux isocyanates, toluene isocyanate (TDI) et diphenylmethane diisocyanate (MDI). Europ.J.Toxicol., 19.., 9, 41-53.

5.2.2 Eye irritation

Species:	Rabbit
Result:	Irritating
Method:	Draize test
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, mixed isomers (unspecified)

RM: 0.1 ml TDI placed in right eye, left eye as control.
3 groups (3 per group), one with unwashed eyes, two with eyes washed after 2 or 4 sec. Eyes observed at 0.5, 1.5, 4 and 8 hours, then daily up to 30 days.

RM: Conjunctival irritation moderate - severe in all groups at 24 hours. Persisted for 10 days in 1st 2 groups but 3rd group less affected at this time. Cornea and iris also affected. In 2 rabbits, corneal opacity persisted for 30 days.
Classed as moderate - severe eye irritant on Draize scale.

RE: Wazeter, F.X. Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI). Eye irritation test in the albino rabbit. International Research & Development Corporation, Report No.100-012, March 13, 1964.

5.2.2 Eye irritation

Species:	Rabbit
Result:	Irritating
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Application to rabbit eye resulted in marked irritation of eyelids and mild damage to corneal epithelium, unless eyes were promptly and thoroughly flushed with water.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.3 Sensitisation

Type:	Open epicutaneous test
Species:	Guinea pig
Result:	Sensitising
Classification:	Sensitising
Method:	Other
Year:	1983
GLP:	No
Test substances:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), dissolved in n-butyl ether.

RM: TDI, 4-40% solutions, applied to clipped dorsum at 2 x 25 µl applications on separate sites, using groups of 5-8 young adult animals. Challenged 5 days later with 6 x 25 µl applications on new sites. Dermal response assessed 24 hours later.

RM: Inductions of 8, 20, 40% TDI and challenges of 0.025 - 0.4% gave scores of 1.6 - 4.0 out of 8.0 on Draize scale, dose-related. Inductions of 4 or 8% TDI and challenge by 0.006 - 0.1% also positive. 4% induction and 0.006 or 0.012% challenge was negative.

RM: Study showed dose dependent skin sensitisation by TDI with a no-effect level established.

RE: Koschier, F.J., Burden, E.J., Brunkhorst, C.S. and Friedman, M.A. Concentration-dependent elicitation of dermal sensitization in guinea pigs treated with 2,4-TDI. Toxicol.Appld.Pharacol., 1983, 67, 401-407.

5.3 Sensitisation

Type:	Other
Species:	Guinea pig
Result:	Sensitising
Classification:	Sensitising
Method:	Other
Year:	1967
GLP;	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4 TDI (CAS No.584-84-9), 1% in dinonyl phthalate.

RM: 0.1 ml TDI solution applied daily to outer ear for 3 days (8 guinea pigs per group). On day 7, 0.2 ml TDI solution applied to clipped flank. Effect evaluated 24 h later.

RM: Ratings on scale ++ (bright pink), + (pink), ± (light pink), Tr (just observable erythema).

RM: Results 1/8 ++, 2/8 +, 2/8 ±, 3/8 trace.
Compound considered to be a skin sensitiser.

RE: Stevens, M.A. Use of the albino guinea-pig to detect the skin-sensitising ability of chemicals. Brit.J.Indstr.Med., 1967, 24, 189-202.

5.3 Sensitisation

Type:	Other
Species:	Guinea pig
Result:	Sensitising
Classification:	Sensitising
Method:	Other
Year:	1967
GLP;	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,6-TDI (CAS No.91-08-7), 1% in dinonyl phthalate.

RM: 0.1 ml TDI solution applied daily to outer ear for 3 days (10 animals per group). On day 7, 0.2 ml TDI solution applied to clipped flank. Effect evaluated 24 h later.

RM: Ratings on scale ++ (bright pink), + (pink), ± (light pink), Tr (just observable erythema).

RM: Results 2/10 ++, 3/10 +, 4/10 ±. 1/10 Tr.
Compound considered to be a skin sensitiser.

RE: Stevens, M.A. Use of the albino guinea-pig to detect the skin-sensitising ability of chemicals. Brit.J.Indstr.Med., 1967, 24, 189-202.

5.3 Sensitisation

Type: Guinea pig maximisation test
Species: Guinea pig
Result: Sensitising
Classification: Sensitising
Method: Other
Year: 1976
GLP: No
Test substsance: Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), 97% purity, 5% in olive oil or Freund's adjuvant.

RM: Method based upon Kligman & Magnusson (1969): See RE.

RM: 1st step: 0.05 ml 5% TDI in olive oil or Freund's adjuvant given id, followed by 1 week rest.
2nd step: 20% TDI in vaseline by dorsal epicutaneous application followed by 1 week rest.
3rd step: 0.1, 0.2 or 0.5% TDI in vaseline applied to flank and left for 24 h. Skin assessed 24 and 48 h later. 3 weeks rest.
Final step: To check possibility of cross sensitisation. 1% MDI in vaseline applied, skin assessed.

RM: oup sizes: 15 females per test group, 6 females per control group (extracted from results information).

RM: Results showed that skin sensitisation occurred when challenged with 0.2 and 0.5% TDI in vaseline at rate of 47% and 72% respectively (no result given for 0.1% TDI in vaseline).
On this basis 2,4-TDI is considered to be a medium - strong skin sensitiser.

RM: Cross sensitisation was shown with MDI when it was applied at 1% in vaseline (82% sensitisation).

RE: DuPrat P, Gradiski D and Marignac B. Pouvoir irritiant et allergisant de deux isocyanates toluene diisocyanate (TDI), diphyenylmethdane diisocyanate (MDI). Europ.J. Toxicol., 1976 9, 41-53.

RE: Using method of: Kligman, B. and Magnusson, A.M. The identification of contact allergens by animal assay, the guinea pig maximisation test, J.Duvertig Derm. 1969, 52, 268-276.

5.3 Sensitisation

Type:	Other
Species:	Guinea pig
Result:	Sensitising
Classification:	Sensitising
Method:	Other
Year:	1981
GLP;	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: DI, 80 : 20 isomer ratio, in olive oil

RM: 50 µl 10% TDI solution applied to shaved dorsal area of each of 8 female guinea pigs. Challenge with 25 µl 0.1% TDI 7 days later by application to one flank of each animal and 25 µl olive oil on other flank.

RM: Contact sensitivity observed in 7/8 animals with maximum severity at 24 hours after challenge. Severity was ++++ on scale of + to ++++.

RE: Karol M.H, Hauth B.A, Riley E.J. and Magreni C.M. Dermal contact with TDI produces respiratory tract hypersensitivity in Guinea Pigs. Toxicol.Appld.Pharmacol., 1981, 58, 221-230.

5.3 Sensitisation

Type:	Mouse ear swelling test
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1985
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80 : 20 isomer ratio, dissolved in ethyl acetate.

RM: Following info. taken from figures and abstract, text is in Japanese.

RM: Mice given application of 1% or 5% TDI solution to tail or back and then challenged 7 days later with 1% TDI solution on ear. Ear thickness measured 24 or 48 hours later.

RM: Significant ear swelling produced by this (modified) procedure.

RE: Tanaka K, Takeoka A, Hanada S, Okamoto Y, Ino T and Okuizumi J. Some additional findings on contact sensititivy of mice induced by TDI. Jpn.J.Allergol, 1985, 34, 128-134.

5.3 Sensitisation

Type:	Mouse ear swelling test.
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1985
GLP:	No
Test Substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (Cas No. 584-84-9) in ethyl acetate.

RM: TDI at concentrations from 0.01 - 10% used to sensitise by applying 100 or 500 µl to shaved abdomen of groups of 5 male mice. Challenged 7 days later by 20 µl of 0.1 or 1% TDI solution on ear. Ear thickness measured 24h later.

RM: Induction with 1-5% TDI and challenge with 1% TDI showed marked response. Challenge with 0.1% TDI showed little or no response.

RM: 100 µl sensitising dose and 20 µl challenge dose using 1% TDI used to investigate effect of age, strain and time on sensitisation response.

RE: Tominaga M, Kohno S, Tanaka K, and Ohata K. Studies on TDI - induced delayed type hypersensitivity. Japan J.Pharmacol., 1985, 39, 163-171.

5.3 Sensitisation

Type:	Mouse ear swelling test
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1980
GLP:	No

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No. 584-84-9) in olive oil.

RM: Groups of 28 hairy or 10 nude mice used.

RM: 30 µl 5% TDI (Hairy) or 30% TDI (nude) solution applied to back daily for 5 days. Mice in both groups challenged with 1% TDI solution applied to ear 4 days later. Ear thickness measured 24 and 48 hours later.

RM: Ear thickness increased 126% at 48h in hairy mice. No effect on nude mice.

RM: Authors suggest thymus - derived T-lymphocytes may have a role in contact sensitisation in hairy mice, since nude mice do not have a thymus.

RE: Yasuda K, Nozawa G, Goto T, Sasaki N and Ishizu S. Experimental studies on TDI dermatitis in mice. J.Toxicol Sci., 1980, 5,11-21.

5.3 Sensitisation

Type:	Mouse ear swelling test.
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1980
GLP:	No
Test Substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No. 584-84-9), in ethyl acetate.

RM: 0.5 ml 5% TDI solution applied to clipped back. Challenged 1 week later with 1% TDI solution on ear. Ear thickness measured after 3, 24, 48 and 72 h.

RM: Highest response shown after 24h, - 100% increase in ear thickness.

RE: Tanaka K. Contact sensitivity in mice induced by tolylene diisocyanate (TDI). J.Dermatol., 1980, 7, 277-280.

5.3 Sensitisation

Type:	Mouse ear swelling test
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified) in acetone.

RM: 0.05 ml Freund adjuvant i.d. followed by 100 µl 5% TDI solution applied topically to stomach of female 6-8 week old mice, 10-15 per group (test), 5-10 per control group. Daily application for 4 days, then challenged 7 days later with topical application 20 µl 0.5% TDI solution to one ear, 20 µl acetone to other ear. Ear thickness measured 24 and 48 hours later.

RM: Strong response in all test animals with ear thickness increasing by 142% on average.

RE: Gad S.C, Dunn BJ, Dobbs D.W, Reilly C. and Walsh R.D. Development and validation of an alternative dermal sensitisation test: The mouse ear swelling test (MEST) Toxicol.Appld.Pharmacol., 1986, 84, 93-114.

5.3 Sensitisation

Type:	Mouse ear swelling test
Species:	Mouse
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80 : 20 isomer ratio, dissolved in acetone

RM: 100 µl TDI solution applied to shaven abdomen of male 6-8 week old mice, 4-5 per group. Challenge after 4 days with 40 µl TDI solution in one ear, 40 µl acetone in other ear. Ear thickness measured 24 hours later.

RM: Dose response shown for sensitising doses of 0.7 - 28 mg/kg TDI. The dose sensitising 50% mice (SD50) was 5.3 mg/kg. Lower responses were obtained with high doses of 149 mg/kg and above.

RM: Cross sensitisation was shown by challenging with other isocyantes - MDI, HDI, HMDI.

RE: Thorne P.S, Hillebrand J.A, Lewis G.R and Karol M.H. Contact sensitivity by diisocyanates: Potencies and cross reactivities. Toxicol.Appld.Pharmacol., 1987, 87, 155-165.

5.3 Sensitisation

Type:	Other
Species:	Rat
Result:	Sensitizing
Classification:	Sensitizing
Method:	Other
Year:	1985
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80 : 20 isomer ratio in ethyl acetate.

RM: Male rats, 7-8 per group, treated as follows: Induction i) 5x100 µl 1% TDI solution to shaved back or ii) 500 µl on shaved tail or iii) to tail as in ii) and then on back 7 days later. Challenge - 7 days after last induction application, 20 µl 1% TDI solution applied to ear. Ear thickness measured 3, 24, 48 and 72 hours later.

RM: Ear swelling response shown by all application methods. Induction by i) or ii) gave maximum response 24 and 48h after challenge. Induction by iii) gave max. response 24h after challenge.

RM: Authors indicate that rat can be used as a model for contact sensitisation.

RE: Tanaka K, Nagaya Y, Marcui S, Okamoto Y and Hanada S. Contact sensitivity in rats induced by TDI. J.Dermatol., 1985, 12, 484-488.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Fischer 344
Sex:	Male/female
Route of Administration:	Gavage
Exposure Period:	14 days
Frequency of Treatment:	Daily
Doses:	30, 60, 120, 240, 500 mg/kg bwt/day 5 males, 5 females per group
Control Group:	Yes concurrent vehicle
NOEL:	60
LOEL:	120 mg/kg/bw/day
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio, in corn oil.

RM: Male and female rats dosed by gavage daily. Rats were 6-7 weeks old at start of dosing and were housed 2-3 per cage.

RM: Rats were observed daily, bodyweight measured on days 0, 7 & 14. Gross examination on all animals.

RS: No dose related mortality. No clinical effect due to treatment. Bodyweight gain depressed 10% or more in males at 120 mg/kg and above, and by 17% in females at 500 mg/kg. No affect on tissues at gross examination.

RE: National Toxicity Program technical report on the toxicology and carcinogenesis studies of commercial grade 2,4(80%) and 2,6(20%) TDI. NIH Publication No.86 - 2507. August 1986.

5.4 Repeated Dose Toxicity

Species:	Mouse
Strain:	B6C3F1
Sex:	Male/female
Route of Administration:	Gavage
Exposure period:	14 days
Doses:	30, 60, 120, 240, 500 mg/kg bwt/day 5 males, 5 females per group
Control Group:	Yes concurrent vehicle
NOEL:	500
LOEL:	>500 mg/kg/bw/day
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ration, in corn oil.

RM: Male and female mice dosed by gavage daily. Mice were 6-7 weeks old at start of dosing and were housed 5 males or 5 females per cage.

RM: Mice were observed daily, bodyweight measured on days 0, 7 and 14. Gross examination on all animals.

RS: No dose related mortality and no effect on clinical condition, bodyweight or on tissues on gross examination.

RE: National Toxicology Program technical report on the toxicology and carcinogenesis studies of commercial grade 2,4(80%) and 2,6(20%) TDI. NIH Publication No.86-2507, August 1986.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Fischer 344/CR
Sex:	Male/female
Route of Administration:	Gavage
Exposure Period:	90 days
Frequency of Treatment:	5 days per week
Doses:	15, 30, 60, 120, 240 mg/kg/bw/day. 10 males, 10 females per group
Control Group:	Yes concurrent vehicle
NOEL:	30
LOEL:	60 mg/kg/bw/dag
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80% 2,4-, 20% 2,6- dissolved in corn oil.

RM: The study was undertaken to provide information for setting dose levels in a subsequent chronic - carcinogenice rat study.

RM: Male and female rats were dosed by gavage at 2.5 ml TDI solution in corn oil per kg bodyweight. Rats were 11 weeks old at start of dosing and were housed 5 males or 5 females per cage.

RM: Rats were observed twice daily, bodyweight measured weekly, gross necropsy all rats, histopathological examination carried out on all control and top dose animals on 28 tissues.

RS: MORTALITY male at 60 mg/kg/day, 2/10 male at 120 mg/kg/day 0 at 240 mg/kg/day. RESPIRATORY 'noise' was heard in 1/10 at 60 mg/kg/day, 1/10 at 120 mg/kg/day and 3/10 at 240 mg/kg/day, mainly in week 7. Bodyweight was depressed by about 10% in males at 120 and 240 mg/kg/day.

RS: Mild and moderate MUCOID BRONCHOPNEUMONIA in 8/10 males at 240 mg/kg/day and moderate-severe in 2/10 females. Less severe lesion in 3/10 males and 1/10 females at 120 mg/kg/day.

RM: As a result of this study, doses of 30 and 60 mg/kg/day for males and 60 and 120 mg/kg/day for females were selected for a 2-year study.

RE: Gordon, E.B. Toluene diisocyanate C50533 subchronic rat study. Litton Bionetics Inc. LBI Project No.10608. August 1978.

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5.4 Repeated Dose Toxicity

Species:	Mouse
Strain:	B6C3F1
Sex:	Male/female
Route of Administration:	Gavage
Exposure period:	90 days
Frequency of treatment:	5 days per week
Doses:	15, 30, 60, 120, 240 mg/kg/bwt/day. 10 males, 10 females per group
Control Group:	Yes concurrent vehicle
NOEL:	60
LOEL:	120 mg/kg/bw/day
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Study undertaken to set dose levels for a subsequent chronic - carcinogenic mouse study.

RM: Male and female mice dosed by gavage at 2.5 ml TDI solution in corn oil per kg bwt. Mice were 10 weeks old at start of dosing and were housed 5 males or 5 females per cage.

RM: Mice were observed twice daily, bodyweight measured weekly, gross examination on all mice dying during the study and on all control and top dose animals on 30 tissues.

RS: MORTALITY of 1/10 female at 120 mg/kg/day and 2/10 females at 240 mg/kg/day. (N.B. there were 25 deaths due to accidental flooding of cages on the last day of study.)

RS: No effect on clinical conditions, bodyweight or tissue histopathology.

RM: Doses of 50 and 100 mg/kg/day suggested for a 2-year study.

RE: Gordon, E.E. Toluene diisocyanate C50533 subchronic mouse study. Litton Bionics Inc. LBI Project No.10608. June 1978.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	-
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	14 days
Frequency of treatment:;	30 min per day, 5 days per week
Doses:	0.34, 2.1, 7.4 ppm. 6 males per group
Control group:	Yes concurrent vehicle
NOEL:	0.34 ppm
LOEL:	2.1 ppm
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Rats exposed in 9 l chambers to TDI vapour in air at concentrations of 0.34, 2.1 or 7.4 ppm. Atmospheres monitored by colorimetric analysis after absorption in 1% DMAB in acetic acid. Rats caged by group during exposure and individually between exposure.

RM: Rats observed before, during and after exposure. Bodyweight before 1st exposure and then weekly. Haematology at days 0, 7, 14 and 21. Gross examination, all rats, microscopic examination of lung, liver and kidney.

RS: No mortality. Signs of PYTALISM in rats at 2.1 and 7.4 ppm. BODYWEIGHT GAIN DEPRESSION at 2.1 and 7.4 ppm.

RE: Wazeter, F.X. PAPI, TDI: Subacute inhalation toxicity study in rats. International Research and Development Corporation, Report No.203-002, December 11, 1964.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Wistar
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	5 days
Frequency of treatment:	4 hours/day
Post Exposure Observ.Period:	14 days
Doses:	0.137, 0.041 mg/l 20 males/group
Control Group:	No
NOEL:	
LOEL:	0.041 mg/l
Method:	other
Year:	1970
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: 20 male rats per group were exposed to TDI in aerosol form by inhalation for 4 h/day for 5 days, at 0.041 or 0.137 mg/l.

RM: The TDI air concentrations were analysed by a colorimetric method after sampling by an impinger.

RM: The rats were observed daily for clinical signs and mortality.

RS: All rats in each group showed treatment related signs of toxicity. These were shown as REDUCED RESPIRATION and EYE AND NOSE IRRITATION. MORTALITY was 1/20 at 0.041 mg/l and 16/20 at 0.137 mg/l.

RE: Kimmerle, G. Desmodur T80, Untersuchungen zur inhalation toxizitat. Bayer, Institute fur Toxikologie report 10 July 1970.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Wistar
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	28 days
Frequency of Treatment	4 hours per day, 5 days per week
Doses:	0.2, 2.0 ppm
Control Group:	Yes concurrent vehicle
NOEL:	0.2 ppm
LOEL:	2.0 ppm
Method:	Other
Year:	1970
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Rats exposed to TDI in aerosol form by inhalation. TDI atmosphere concentrations analysed by a colorimetric method after sampling by an impinger.

RM: Rats observed daily, bodyweight weekly, clinical chemistry on 10 rats per group at termination, haematology on 5 rats per group, gross examination on all rats and organ weights.

RS: Two rats died at 2 ppm. LABOURED BREATHING in rats t 2 ppm, also depressed bodyweight gain. There was severe LUNG DAMAGE at 2 ppm, accompanied by marked increase in LUNG WEIGHT. No effect on biochemistry or haematology. No effects at 0.2 ppm.

RE: Kimmerle, G. Desmodur T80, Untersuchungen zur inhalation toxizitat. Bayer, Institute fur Toxikologie report 10 July 1970.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Wistar
Sex:	Male/female
Route of Administration:	Inhalation
Exposure period:	21 days
Frequency of treatment:	6 hours per day, 5 days per week
Doses:	0.24, 0.67, 2.83 ppm. 8 males, 8 females per group.
Control group:	Yes concurrent vehicle
NOEL:	Not obtained
LOEL:	0.24 ppm
Method:	Other
Year:	1980
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Male and female rats, 175-215g, exposed to TDI vapour at air concentrations of 0, 0.24, 0.67 or 2.83 ppm. Animals were housed individually during exposure and 4 per cage between exposures. Airflow through the 60 l chambers was 8 l per minute.

RM: Atmosphere concentrations were measured by drawing air through glass absorbers containing absorbing solution, followed by colorimetric analyses. Three analyses for each level during each exposure.

RM: Animals were examined for clinical condition, bodyweight, food and water consumption, lung function (weekly), haematology, blood and urine biochemistry (at termination), gross and microscopic tissue examination.

RS: All rats at lowest level showed LABOURED BREATHING at days 7/8 when atmosphere concentration showed excursion to 0.6 ppm. LABOURED BREATHING occurred in all rats at 0.67 ppm and was severe at 2.84 ppm. Four rats DIED or were killed at 2.83 ppm (1/8 male, 3/8 female).

RS: Effects seen at 2.83 ppm included decreased RESPIRATION RATE and TIDAL VOLUME, increased AIRWAY RESISTANCE, decreased URINE VOLUME and PROTEIN, increased BLOOD UREA, increased HAEMOGLOBIN, HAEMATOCRIT, RED CELL COUNT, decreased WHITE CELL COUNT and PLATELET COUNT.

RS: BODYWEIGHT LOSS occurred in males and females at 2.83 ppm after the 5th day of exposure and was related to decreased FOOD INTAKE.

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RS: Histopathological changes at 2.83 ppm occurred in NASAL PASSAGES as marked EPITHELIAL RHINITIS with varying degrees of REPARATIVE EPITHELIAL HYPERPLASIA. In the LARYNX, FOCAL EPITHELIAL NECROSIS/ DEGENERATION was seen in 2/8 males and 3/8 females. REPARATIVE EPITHELIAL HYPERPLASIA was the major change in the TRACHEA (4/8 males, 6/8 females). Several effects occurred in the lungs, affecting some or all rats, these were: slight-moderate NECROTISING BRONCHITIS or BRONCHIOLITIS and BRONCHIAL/BRONCHIOLAR EPITHELIAL HYPERPLASIA and SQUAMOUS METAPLASIA, ALVEOLAR OEDEMA and HISTIOCYTOSIS accompanied by EPITHELIALISATION, ACUTE ALVEOLITIS and CHRONIC INTERSTITIAL INFILTRATION and FIBROSIS.

At 0.67 ppm, similar but less severe and less frequent histopathological changes were seen in the LARYNX, TRACHEA, LUNG and NASAL PASSAGES. At 0.24 ppm, REPARATIVE EPITHELIAL HYPERPLASIA (1/8 male, 2/8 female) and SQUAMOUS METAPLASIA (1/8 male, 3/8 female) occurred in the LARYNX. Most rats showed EPITHELIAL DEGENERATION with MILD-MODERATE ACUTE RHINITIS of the NASAL PASSAGES, minimal changes were seen in the LUNG mainly as FOCAL ALVEOLAR HISTIOCYTOSIS (1/8 male, 2/8 female).

RM: Atmospheric levels were difficult to control at the lowest level and effects seen may have been due to high (up to 0.6 ppm) excursions.

RE: Bennett, I.P., Chart, J.S., Doe, J.E., Gore, C.W. and Patton, D.S.G. Tolylene Diisocyanate, Three Week Inhalation Toxicity in the Rat. ICI Central Toxicology Laboratory Report No.CTL/T/1286, 2 February 1980.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	Fischer 344
Sex:	Male/female
Route of Administration:	Inhalation
Exposure period:	30 days
Frequency of treatment:	6 hours per day for 20-22 exposure days
Doses:	0.1, 0.3 ppm. 10 males, 10 females per group
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.1 ppm
Method:	Other
Year:	1976
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Rats exposed to TDI vapour at air concentrations of 0.1 and 0.3 ppm in 14.5 m^3 chambers. Test atmosphere analysed by the Marcali method.

RM: Rats observed daily, bodyweight measured twice weekly. Haematology and blood biochemistry at termination. Gross examination on all animals. Livers and kidneys weighed.

RS: No mortality. Respiratory and eye irritation in all groups did not seem to be related to treatment. BODYWEIGHT GAIN was significantly DECREASED in males at 0.3 ppm and to a lesser extent at 0.1 ppm.

RS: There were no changes in haematology, blood biochemistry, organ weight or gross pathology that could be considered to be due to treatment.

RE: Henck, J.W., Kociba, R.J., Keyes, D.G. and McKenna, M.J. A 30-day repeated inhalation toxicity study of TDI in laboratory animals. Dow Chemical Co., Midland, Michigan, February 25, 1976.

5.4 Repeated Dose Toxicity

Species:	kat
Strain:	Sprague-Dawley
Sex:	Male/female
Route of Administration:	Inhalation
Exposure period:	30 days
Frequency of treatment:	6 hours per day, for 20-22 exposure days
Doses:	0.1, 0.3 ppm 10 males, 10 females per group
Control group:	Yes concurrent vehicle
NOEL;	0.1 ppm
LOEL:	0.3 ppm
Method:	Other
Year:	1976
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Rats exposed to TDI vapour at air concentration of 0.1-0.3 ppm in 14.5 m^3 chambers. Test atmospheres analysed by the Marcali method.

RM: Rats observed daily, bodyweight measured twice weekly. Haematology of blood biochemistry at termination. Gross examination on all animals. Livers and kidneys weighed.

RS: No mortality. Respiratory irritation seen in rats in all groups including control. Probably due to a glandular infection. However, 0.3 ppm group were affected most and did not recover to same extent as other groups. The 0.3 ppm males showed DECREASED BODYWEIGHT GAIN which may have been accentuated by the infection.

RS: Lesions of the salivary glands and eyes in males were considered to be due to the glandular infection. Increased amount of CATARRHAL MATERIAL in NASAL TURBINATES of 1/10 male rats at 0.3 ppm was considered to be only lesion due to compound exposure.

RS: No effect on haematology, blood biochemistry or organ weight.

RE: Henck, J.W., Kociba, R.J., Keyes, D.G. and McKenna, M.J. A 30-day repeated inhalation toxicity study of TDI in laboratory animals. Dow Chemical Co., Midland, Michigan, February 25, 1976.

5.4 Repeated Dose Toxicity

Species:	Mouse
Strain:	CD-1
Sex:	Male/female
Route of Administration:	Inhalation
Exposure period:	30 days
Frequency of treatment:	6 hours per day, for 20-22 exposure days
Doses:	0.1, 0.3 ppm. 10 males, 10 females per group
Control group:;	Yes concurrent vehicle
NOEL:	0.3 ppm
LOEL:	>0.3 ppm
Method:	Other
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Mice exposed to TDI vapour at air concentrations of 0.1 and 0.3 ppm in 14.5 m^3 chambers. Test atmospheres analysed by the Marcali method.

RM: Mice observed daily, bodyweight measured twice weekly. Haematology and blood biochemistry at termination. Gross examination on all animals. Livers and kidneys weighed.

RS: One male mouse died on 1st day of exposure at 0.3 ppm but no indication that this was due to treatment. No effect on clinical condition, bodyweight, haematology, blood biochemistry, organ weight or gross pathology due to treatment.

RE: Henck, J.W., Kociba, R.J., Keyes, D.C. and McKenna, M.J. A 30-day repeated inhalation toxicity study of TDI in laboratory animals. Dow Chemical Co., Midland, Michigan, February 25, 1976.

5.4 Repeated Dose Toxicity

Species:	Hamster
Strain:	Golden Syrian
Sex:	Male/female
Route of Administration:	Inhalation
Exposure period:	30 days
Frequency of treatment:	6 hours per day, for 20-22 exposure days
Doses:	0.1, 0.3 ppm.
	10 males, 10 females per group
Control group:	Yes concurrent vehicle
NOEL:	0.1
LOEL:	0.3 ppm
Method:	Other
Year:	1976
GLP:	No
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Hamsters exposed to TDI vapour at air concentrations of 0.1 and 0.3 ppm in 14.5 m^3 chambers. Test atmospheres analysed by the Marcali method.

RM: Hamsters observed daily, bodyweight measured twice weekly. Haematology and blood biochemistry at termination. Gross examination of all animals. Livers and kidneys weighed. Subsequent histophatholgical examination of liver, kidney, lungs and nasal turbinates from 5 hamsters/sex at each exposure level and control (see RE).

RS: No mortality and no effects on clinical condition, bodyweight, haematology, blood biochemistry or organ weight.

RS: Increased incidence of FOCAL HYPERPLASIA of RESPIRATORY EPITHELIUM of NASAL TURBINATES, accompanied by slight INFLAMMATION, in the 5 males, 5 females at 0.3 ppm. Also PERIBRONCHIOLAR AGGREGATE of PRIMARY MONONUCLEAR CELLS in LUNGS of some of these animals.

RE: Henck, J.W., Kociba, R.J., Keyes, D.G. and McKenna, M.J. A 30-day repeated inhalation toxicity study of TDI in laboratory animals. Dow Chemical Co., Midland, Michigan, February 25, 1976.

RE: Kociba, R.J., Keyes, D.G. and Wolfe, E.L. Histopathological observations in seelcted tissues of Syrian hamsters exposed by inhalation to vapors of TDI for 6 hours/day, 5 days/week for 4 weeks. Dow Chemical Co., Midland, Michigan, September 27, 1979.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	266 days
Frequency of treatment:	6 hours per day, 1 day per week for 38 weeks
Doses:	0.1 ppm, 10 rats per group.
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.1 ppm
Method:	Other
Year:	1965
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RS: TDI (unspecified)

RM: Rats exposed to TDI vapour in 25 cubic feet chambers. Atmospheres analysed by the Marcali method.

RM: Rats observed at frequent intervals. Microscopic examination on tissues of surviving animals.

RS: During first 30-90 min of exposure, all animals showed GENERAL DISCOMFORT and HYPERACTIVITY which continued for 3-4 hours after exposure. The animals then became LETHARGIC. RALES were heard in about 1/3rd rats after 8 exposures and in most after 12 exposures/

RS: All exposed rats showed PNEUMONITIS to varying degree in lungs. Mostly as mild-moderate TRACHEITIS and BRONCHITIS often accompanied by varying degrees of BRONCHOPNEUMONIA. 6/10 rats showed PROLIFERATION of FIBROUS TISSUE in walls of BRONCHIOLES.

RE: Niewenhuis, R., Scheel, L., Stemmer, K. and Killens,R. Toxicity of chronic low level exposures to TDI in animals. Am.Ind.Hyg.Assoc.J., 1965 26, 143-149.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	78 days
Frequency of treatment:	6 hours per day, 5 days per week for 58 exposures
Doses:	0.1 ppm. 18 rats per group
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.1 ppm
Method:	Other
Year:	1965
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TW)

RS: TDI (unspecified)

RM: Rats exposed to TDI vapour 25 cub.ft. chambers. Atmospheres analysed by Marcali method.

RM: Rats observed at frequent intervals. Groups were sacrificed immediately and 3, 10, 20 and 24 days after last exposure. Tissues examined microscopically.

RS: During 1st 30-90 min of exposure all animals showed GENERAL DISCOMFORT and HYPERACTIVITY which continued for 2-3 h after exposure. The animals then became LETHARGIC. RALES were heard in about 1/3rd rats after 8 exposures and in most after 13 exposure.

RS: Immediately after the last exposure only a few foci of mild bronchopneumonia and bronchitis were present. After 3 days the presence of inflammation was more pronounced. 3/5 rats had BRONCHIECTASIS with marked chronic and acute INFLAMMATION and areas of BRONCHOPNEUMONIA. After 20 and 24 days 5/6 rats showed PURULENT BRONCHIECTASIS with areas of BRONCHOPNEUMONIA and chronic TRACHEITIS.

RM: Control rats also showed moderate to marked bronchiectasis with peribronchitis and peribronchiolotis, similar to chronic murine pneumonia.

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5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Rat
Exposure time:	4 hours
Value:	13.9 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: Study in 2 parts i) mortality assessment at 0.1-34 ppm TDI
ii) pathology assessment of respiratory tract up to 28 days after single 4 h exposure of 2, 5 or 10 ppm TDI.

RM: TDI generated as an aerosol. Atmospheric monitored by Marcali method.

RM: Clinical signs included lacrimation, salivation and general discomfort proportional to exposure concentration.

RM: Pathological effect at 2 ppm limited in lung, with recovery by 7 days after exposure.
5 and 10 ppm produced severe changes in lung and trachea.
Bronchopneumonia developed at various stages after exposure.

RE: Duncan, B., Scheel,L.D., Fairchild, E.J., Killens, R. and Graham, S. Toluene diisocyanate inhalation toxicity: pathology and mortality. Am.Ind.Hyg.Assoc.J., 1962, 23, 447-456.

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Mouse
Exposure time:	4 hours
Value:	9.7 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: Study in 2 parts i) mortality assessment at 0.1-34 ppm TDI.
ii) pathology assessment of respiratory tract up to 28 days after single 4 h exposure to 2, 5 or 10 ppm TDI.

RM: TDI generated as an aerosol. Atmospheres monitored by Marcali method.

RM: Clinical signs included lacrimation, salivation and general discomfort proportional to exposure concentration.

RM: Pathological effect in lungs at 2 ppm in only 2/30 mice.
5 and 10 ppm produced severe effects in lungs, severity dependent upon concentration of TDI.

RE: Duncan, B., Scheel, L.D., Fairchild, E.J., Killens, R. and Graham, S. Toluene diisocyanate inhalation toxicity: pathology and mortality. Amer.Ind.Hyg.Assoc.J., 1962, 23, 447-456.

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5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Guinea Pig
Exposure time:	4 hours
Value:	12.7 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: Study in 2 parts i) mortality assessment at 0.1-34 ppm TDI.
ii) pathology assessment of respiratory tract up to 28 days after single 4 h exposure to 2, 5 or 10 ppm TDI.

RM: TDI generated as an aerosol. Atmosphere monitored by Marcali method.

RM: Clinical signs included lacrimation, salivation and general discomfort proportional to exposure concentration.

RM: Pathological effects at 2 ppm limited in lung, with recovery 7 days after exposure.
5 and 10 ppm produced severe changes in lung and trachea. Bronchopneumonia developed at various stages.

RE: Duncan, B., Scheel, L.D., Fairchild, E.J., Killens, R. and Graham, S. Toluene diisocyanate inhalation toxicity: pathology and mortality. Am.Ind.Hyg.Assoc.J., 1962, 23, 447-456.

5.1.2 Acute Inhalation Toxicity

Type:	LC50
Species:	Rabbit
Exposure time:	4 hours
Value:	11.0 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI (unspecified)

RM: Study in 2 parts i) mortality assessment at 0.1 - 34 ppm TDI
ii) pathology assessment of respiratory tract up to 28 days after single 4 h exposure to 2, 5 or 10 ppm TDI.

RM: TDI generated as an aerosol. Atmospheres monitored by Marcoli method.

RM: Clinical signs included lacrimation, salivation and general discomfort proportional to exposure concentration.

RM: Pathological effect at 2 ppm limited in lung with recovery in 7 days after exposure.
5 and 10 ppm produced severe changes in lung and trachea.
3 animals died at day 4 at 10 ppm. Bronchopneumonia developed at various stages after exposure.

RE: Duncan, B., Scheel, L.D., Fairchild, E.J., Killens, R. and Graham, S. Toluene diisocyanate inhalation toxicity: pathology and mortality. Am.Ind.Hyg.Assoc.J., 1962, 23, 447-456.

5.1.2 Acute Inhalation Toxicity

Type:	Other - RD50
Species:	Mouse
Exposure time:	3 hours
Value:	0.26 ppm
Method:	Other
Year:	1982
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,6 TDI (CAS No.91-08-7)

RM: Male mice; 24-27 g bodyweight, 4 per group, exposed to TDI vapour at concentrations of 0.05-1.1 ppm. Head only exposure.

RM: Atmosphere analysed using Marcali method.

RM: Respiratory rate measured before, during and after exposure.

RM: Respiratory rate decreased with time and increased concentration.

RE: Weyel, D.A., Rodney, B.S. and Alarie, Y. Sensory irritation, pulmonary irritation and acute lethality of a polymeric isocyanate and sensory irritation of 2,6 TDI. Toxicol.Appld.Pharmacol., 1982. 64, 423-430.

5.1.2 Acute Inhalation Toxicity

Type:	Other - RD50
Species:	Mouse
Exposure time:	4 hours
Value:	0.199 ppm
Method:	Other
Year:	1979
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Male mice, 24-27 g bodyweight, 4 per group, exposed to TDI vapour at concentrations of 0.007 - 3 ppm. Head only exposure.

RM: Atmospheres analysed by Marcali method.

RM: Respiratory rate measured before, during and after exposure.

RM: Effect on respiratory rate was concentration and time dependent. Recovery was dependent upon exposure duration, i.e. short exposure - quick recovery long exposure - slow recovery.

RE: Sangha, G.K., and Alarie, Y. Sensory irritation by Toluene diisocyanate in single and repeated exposures. Toxicol.Appld. Pharmacol. 1979, 50, 533-547.

5.1.3 Acute Dermal Toxicity

Type:	Other - see RM
Species:	Rabbit
Value:	
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Doses as big as 16,000 mg/kg failed to kill or produce injury to organs:

RM: Severe local skin irritation.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archive Ind.Hlth., 1957, 15, 324-330.

5.1.3 Acute Dermal Toxicity

Type:	LD50
Species:	Rabbit
Value:	>9400 mg/kg
Method:	Other
Year:	1964
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, isomer ratio and purity not specified.

RM: TDI applied undiluted to intact or abraded skin of 2 male and 2 female rabbits at doses of 2500-9400 mg/kg. 24 hour contact, 14 day observation.

RM: No observed systemic toxicity.
Moderate - marked skin irritation according to dose.

RE: Wazeter, F.X. Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI). Acute dermal toxicity studies (LD50) in the albino rabbit. International Research & Development Corporation, Report 100-012, January 27, 1964.

5.2.1 Skin Irritation

Species:	Rabbit
Result:	Moderately irritating
Method:	Draize test
Classification:	Irritating
Year:	1976
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI, 97% purity (CAS No.584-84-9)

RM: 0.5 ml TDI applied to intact or abraded skin of female rabbits, 6 per group, and occluded for 24 h. Skin examined 24, 48 and 72 hours later. Also macroscopic and microscopic examination up to 10 days.

RM: At 24 hours - oedema slight 2/6, moderate 3/6, severe 1/6. Slight regression by 72 h. Results similar from abraded skin. Primary cutaneous irritation index of 3.6 on a 0-8 scale. Resolution in 3 weeks.

RE: Duprat, P., Gradiski, D. and Marignac, B. Pouvoir irritant et allergisant de deux isocyanates, toluene diisocyanate (TDI) et diphenylmethane diisocyanate (MDI). Europ J.Toxicol., 1976, 9, 41-53.

RE: Nievenhuis, R., Scheel, L., Stemmer, K. and Killens, R. Toxicity of chronic low level exposures to TDI in animals. Am.Ind.Hyg.Assoc.J., 1965, 26, 143-149.

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5.4 Repeated Dose Toxicity

Species:	Rabbit
Strain:	
Sex:	No data
Routes of Administration:	Inhalation
Exposure period:	266 days
Frequency of treatment:	6 hours per day, 1 day per week for 38 weeks
Doses:	0.1 ppm. 3 rabbits per group
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.1 ppm
Method:	Other
Year:	1965
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Rabbits exposed to TDI vapour in 25 cub.ft. chambers. Atmospheres analysed by the Marcali method.

RM: Rabbits observed at frequent intervals. Microscopic examination on tissues of surviving animals.

RS: During 1st 30-90 min of exposure all animals showed GENERAL DISCOMFORT and HYPERACTIVITY which diminished before exposure ended. Towards end of study some rabbits showed SPASTIC-LIKE BREATHING and LIMB MOVEMENT during exposure.

RE: Niewenhuis, R., Scheel, L., Stemmer, K. and Killens, R. Toxicity of chronic low level exposures to TDI on animals. Am.Ind.Hyg.Assoc.J., 1965, 26, 143-149.

5.4 Repeated Dose Toxicity

Species:	Rabbit
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	78 days
Frequency of treatment:	6 hours per day, 5 days per week for 58 exposures
Doses:	0.1 ppm. 6 rabbits per group.
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.1 PPM
Method:	Other
Year:	1965
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Rabbits exposed to TDI vapour in 25 cub.ft chambers. Atmospheres analysed by Marcali method.

RM: Rabbits observed at frequent intervals. Groups were sacrificed immediately and 3, 10, 20 and 24 days after last exposure. Tissues examined microscopically.

RS: Two rabbits died.

RS: During 1st 30-90 min of exposure all animals showed GENERAL DISCOMFORT and HYPERACTIVITYY which diminished before exposure ended. Towards end of study some rabbits showed SPASTIC-LIKE BREATHING and LIMB MOVEMENT during exposure.

RS: 3 days after last exposure lungs showed areas of BRONCHOPNEUMONIA and subacute-chronic BRONCHITIS. After 10 days there was extensive INFLAMMATORY involvement. At 20 days chronic BRONCHITIS was the only major abnormality.

RE: Niewenhuis, R., Scheel, L., Stemmer, K. and Killens, R. Toxicity of chronic low level exposures to TDI in animals. Am.Ind.Hyg.Assoc.J., 1965, 26, 143-149.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	78 days
Frequency of treatment:	6 hours per day, 5 days per week for 58 exposures
Doses:	0.1 ppm, 9 guinea pigs per group
NOEL:	
LOEL:	0.1 ppm
Method:	Other
Year:	1965
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Guinea pigs exposed to TDI vapour in 25 cu.ft chamber. Atmospheres analysed by Marcali method.

RM: Guinea pigs observed at frequent intervals. Groups were sacrificed immediately and 3,10, 20 and 24 days after last exposure. Tissues examined microscopically.

RS: 4 guinea pigs died.

RS: During 1st 30-90 min of exposure all animals showed GENERAL DISCOMFORT and HYPERACTIVITY which diminished before exposure ended.

RS: Lungs showed focal accumulation of lymphocytes, macrophages and plasma cells, often in close association with small blood vessels and bronchioles. INFLAMMATION varied from SLIGHT DIFFUSE to PROMINENT PNEUMONITIS with BRONCHOPNEUMONIA.

RE: Niewenhuis, R., Scheel, L., Stemmer, K. and Killens, R. Toxicity of chronic low level exposures to TDI in animals. Am.Ind.Hyg.Assoc.J., 1965, 26, 143-149.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2, 3 or 5 days
Frequency of treatment:	6 hours per day.
Doses:	9.5 ppm (2 days), 9.6 ppm (3 days) 5 rats/group. 9.25 ppm (5 days) 10 rats/group
Control group:	No data specified
NOEL:	
LOEL:	9.25 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4 TDI (CAS No.584-84-9)

RM: Rats exposed to TDI aerosol for periods of 2, 3 or 5 days. Atmospheres analysed by Marcali method.

RM: Rats observed during exposure period and after. Tissues examined microscopically.

RS: All rats died, with average survival time of 5 days. All showed severe signs of eye and nasal passage IRRITATION. Death due to blockage of RESPIRATORY PASSAGES with separated mucosa from bronchi and trachea. Microscopic examination showed severe PERIBRONCHITIS and BRONCHOPNEUMONIA.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2, 3 or 5 days
Frequency of treatment:	6 hours per day
Doses:	10.4 ppm (2 or 3 days), 5 rats/group 10.45 ppm (5 days), 10 rats/group
Control group:	No data specified
NOEL:	
LOEL:	10.4 PPM
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,6-TDI (CAS No.91-08-7)

RM: Rats exposed to TDI aerosol for periods of 2, 3 or 5 days. Atmospheres analysed by Marcali method.

RM: Rats observed during exposure period and after. Tissues examined microscopically.

RS: 5/5 and 10/10 rats died after 3 or 5 days exposure respectively and 4/5 after 2 days exposure. Average survival time of about 6 days. All rats showed severe signs of eye and nasal passage IRRITATION. Death due to blockage of RESPIRATORY PASSAGES with separated mucosa from bronchi and trachea. Microscopic examination showed severe PERIBRONCHITIS and BRONCHOPNEUMONIA.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2, 3 or 5 days
Frequency of treatment:	6 hours per day
Doses:	10.6 ppm. 5 rats/group (2 or 3 days) 10 rats/group (5 days)
Control group:	No data specified
NOEL:	
LOEL:	10.6 PPM
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 65:35 isomer ratio

RM: Rats exposed to TDI aerosol for periods of 2, 3 or 5 days. Atmospheres analysed by Marcali method.

RM: Rats observed during exposure period and after. Tissues examined microscopically.

RS: All rats died, with average survival time of about 5 days. All showed severe signs of eye and nasal passage IRRITATION. Death due to blockage of RESPIRATORY PASSAGES with separated mucosa from bronchi and trachea. Microscopic examination showed severe PERIBRONCHITIS and BRONCHOPNEUMONIA.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration	Inhalation
Exposure period:	4 days
Frequency of treatment:	6 hours per day
Doses:	4.5 ppm 20 rats per group
Control group:	No data specified
NOEL:	
LOEL:	4.5 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 65:35 isomer ratio

RM: Rats exposed to TDI aerosol for 4 days. Atmosphere analysed by Marcali method.

RM: Rats observed during exposure period and after. Tissues examined microscopically.

RS: 13/20 rats died, with average survival time of about 6.5 days. The 7 surviving rats were observed for 4 weeks. Severe signs of RESPIRATORY IRRITATION seen in all animals. Microscopic examination showed severe BRONCHOPNEUMONIA.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	12 days
Frequency of treatment:	6 hours per day, 10 exposures
Doses:	0.95 ppm, 20 rats/group
Control group:	No data specified
NOEL:	
LOEL:	0.95 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI 65:35 isomer ratio

RM: Rats exposed to TDI aerosol for 10 daily exposures over a period of 12 days. Atmosphere analysed by the Marcali method.

RM: Rats observed during the exposure period and after tissues examined microscopically.

RS: 15/20 rats died, the first after 4 days. Lungs from surviving animals were examined 73-121 days after the last exposure.

RS: Lungs showed severe PERIBRONCHITIS and BRONCHOPNEUMONIA due to exposure, with partial reversal several months after the last exposure.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2 x 14 days
Frequency of treatment:	6 hours per day, 6 days per week for 2 weeks, repeated after a 4-week break.
Doses:	0.48 ppm, 20 rats per group
Control group:	No data specified
NOEL:	
LOEL:	0.48 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 65:35 isomer ratio

RM: Two groups of 20 rats of bodyweights 91-124 g and 140-184 g, exposed to TDI aerosol for 2 weeks (12 exposures) followed by a 4-week break and then another 2-week exposure period. Atmospheres analysed by the Marcali method.

RM: Rats observed during the exposure period and after. Tissues examined microscopically.

RS: 9/20 of the group initially weighing 91-124 g died during and just after the first 2 weeks exposure period (1st death at day 8). No mortality in the group of heavier rats.

RS: Microscopic examination of lungs showed PERIBRONCHITIS and BRONCHOPNEUMONIA at day 41, i.e. 4 weeks after the end of the 1st exposure period and at day 59, i.e. 4 days after the 2nd exposure period ended. These effects showed reversal to normal findings 8 weeks after the last exposure.

RE: Henschler, D., Assman, W. & Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rats
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2 x 28 days
Frequency of treatment:	6 hours per day, 5 days per week for 4 weeks, repeated after a 4-week interval.
Doses:	0.11 ppm. 30 rats/group
Control group:	Yes concurrent no treatment
NOEL:	
LOEL:	0.11 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 65:35 isomer ratio

RM: A group of 30 rats, initial bodyweight 140-185 g, exposed to TDI aerosol for 4 weeks (20 exposures) followed by a 4-week interval and then another 4 week exposure period. Atmospheres analysed by the Marcali method.

RM: Rats observed during and after exposure periods. Bodyweight measured at intervals throughout study. Microscopic examination of tissue at termination.

RS: No mortality. Bodyweight of exposed rats was lower than controls during 1st 4-week exposure period, then returned almost to control level at the end of the 4-week interval and was again reduced below control value during the 2nd 4-week exposure period. Microscopic lung changes were similar to those in controls.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zum Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2 x 14 days
Frequency of treatment:	6 hours per day, 5 days per week for 2 weeks, repeated after a 4-week break.
Doses:	0.49 ppm. 5 animals/group
Control group:	No data specified
NOEL:	
LOEL:	0.49 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remarks (RM), Results (RS), Test substances (TS)

TS: TDI, 65:35 isomer ratio

RM: Guinea pig, 395-480 g initial bodyweight, exposed to TDI aerosol. Atmosphere analysed by Marcali method. Animals observed during and after exposure.

RS: 2/5 animals died, one after 10 days, the other after 11 days, of the 1st exposure period.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 19, 364-389.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	2 x 28 days
Frequency of treatment:	6 hours per day, 5 days per week for 4 weeks, repeated after a 4-week interval
Doses:	0.11 ppm. 5 animals/group
Control group:	Yes concurrent no treatment
NOEL:	
LOEL:	0.11 ppm
Method:	Other
Year:	1962
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TSW)

TS: TDI, 65:35 isomer ratio

RM: Guinea pigs, 375-412 g initial bodyweight, exposed to TDI aerosol. Atmospheres analysed by Marcali method.

RM:: Animals observed during and after exposure, bodyweight measured at intervals throughout study.

RS: No mortality. Bodyweight of exposed animals was slightly reduced compared to controls during the 1st exposure period and the 4-week interval and then was more depressed during the 2nd exposure period.

RE: Henschler, D., Assman, W. and Meyer, K.O. Zur Toxikologie der Toluylendiisocyanate. Arch.Toxikol., 1962, 364-389.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	10 or 30 days
Frequency of treatment:	6 hours per day
Doses:	1-2 ppm
Control group:	No data specified
NOEL:	
LOEL:	1 PPM
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RS: No observable effect. Microscopic evidence of TRACHEOBRONCHITIS.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.4 Repeated Dose Toxicity

Species:	Rat
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	79 days
Frequency of treatment:	6 hours per day
Doses:	1.5 ppm 5 rats/group
NOEL:	
LOEL:	1.5 ppm
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RS: No mortality. 4/5 rats showed varying degrees of BRONCHITIS at termination.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.4 Repeated Dose Toxicity

Species:	Rabbit
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	3-71 days
Frequency of treatment:	6 hours per day
Doses:	1.5 ppm
Control group:	No data specified
NOEL:	
LOEL:	1.5 ppm
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: 5 rabbits exposed to TDI for up to 71 exposures.

RS: One rabbit died after 3 and one died after 5 exposures. A third rabbit was killed after 19 exposures, another after 52 and the fifth after 71 exposures. All animals showed BRONCHITIS.

RE: Zapp, J.A. Hazards of isocyanates in polyurthane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	
Sex:	No data
Route of Administration:	Inhalation
Exposure period:	23-78 days
Frequency of treatment:	6 hours per day
Doses:	1.5 ppm
Control group:	No data specified
NOEL:	
LOEL:	1.5 ppm
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RS: Guinea pigs killed after 23, 40, 57, 61 and 79 exposures. All showed BRONCHITIS and varying degrees of BRONCHIAL PNEUMONIA.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.4 Repeated Dose Toxicity

Species:	Dog
Strain:	
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	120 days
Frequency of treatment:	0.5-2 hours per day for total of 35-37 exposures
Doses:	1.5 ppm
Control group:	No data specified
NOEL:	
LOEL:	1.5 ppm
Method:	Other
Year:	1957
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RS: Signs of LACRIMATION, COUGHING, RESTLESSNESS during exposure.

Blood pressure, heart rate, respiration rate, bodyweight, blood chemistry, haematology, were not affected.

RS: At termination, MILD CONGESTION and INFLAMMATION of TRACHEA and LARGE BRONCHI. Thick mucous plugs in some of bronchial branches.

RE: Zapp, J.A. Hazards of isocyanates in polyurethane foam plastic production. Amer.Med.Assocn.Archives Ind.Hlth, 1957, 15, 324-330.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	
Sex:	Male
Route of Administration:	Inhalation
Exposure Period:	5 days
Frequency of treatment:	4 h per day
Post Exposure Obsv.Period:	21 days
Doses:	3.1 ppm, 10 animals per group
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	3.1 ppm
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Male English Short Hair guinea pigs were exposed to TDI vapour. Atmospheres analysed by Marcali method.

RM: Animals killed at 2, 24, 72 hours and 1 and 3 weeks after last exposure. Trachea at right carina, right main stem bronchus and right mid-clavicular middle lung removed for microscopic and electron microscopic examination.

RS: Considerable damage to EPITHELIUM, with stratified non-keratinizing cells lining the airways during first week after last exposure. Recovery almost complete 3 weeks after exposure ceased. Moderate increase in Type II cells in peripheral lung.

RE: Miller, M.L., Andringa, A., Vinegar, A., Adams, W.D. Cibulas, W. and Brooks, S.M. Morphology of tracheal and bronchial epithelium and Type II cells of the peripheral lung of the guinea pig after inhalation of TDI vapors. Exptl.Lung Res. 1986, 11, 145-163.

5.4 Repeated Dose Toxicity

Species:	Guinea pig
Strain:	Hartley
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	14 days
Frequency of treatment:	5 hours per day, 5 days per week
Doses:	0.03, 0.26 ppm 7-8 per group
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.03 ppm
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Male guinea pigs, 300-350g bodyweight, were exposed to TDI vapour. The atmospheres were monitored by the Marcali method.

RM: Animals were killed immediately after the last exposure and the trachea at the carina, right main stem bronchus and right mid-clavicular middle lung removed for microscopy and electron microscopy.

RS: At both exposure levels there was a pattern of INFOLDING of the surface of the EPITHELIUM which was more apparent than in controls. CYST-LIKE STRUCTURES also demonstrated, and were twice control incidence in bronchus at 0.03 ppm and 5 and 3 times control level in bronchus and carina respectively. No inflammation was evident.

RE: Miller, M.L., Andringa, A., Vinegar, A., Adams, W.D., Cifulas, W. and Brooks, S.M. Morphology of tracheal and bronchial epithelium and Type II cells of the peripheral lung of the guinea pig after inhalation of TDI vapor. Exptl.Lung.Res., 1986, 11, 145-163.

5.4 Repeated Dose Toxicity

Species:	Mouse
Strain:	Swiss - Webster
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	5 days
Frequency of treatment:	6 hours per day
Post Exposure Observ.Period:	3 days
Doses:	0.4 ppm, 16-24 per group.
Control group:	Yes concurrent vehicle
NOEL:	
LOEL:	0.4 ppm
Method:	Other
Year:	1984
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS; TDI (unspecified)

RM: Male mice, 25-30 g, were exposed to TDI vapour in 102 litre chambers. Atmospheres were analysed by a modified Marcali method.

RM: Half the mice were killed immediately after the last exposure, the remainder about 3 days later. Nasal passage, trachea and lungs removed for microscopic examination.

RS: Lesions produced in upper respiratory tract included INFLAMMATION, ULCERATION, SQUAMOUS METAPLASIA. Recovery was minimal - moderate and not complete within 3 days post-exposure.
No effect on lungs or trachea.

RE: Buckley, L.A., Jiang, X.Z., James, R.A., Morgan, K.T. and Barrow, C.S. Respiratory tract lesions induced by sensory irritants at the RD50 concentration. Toxicol.Appld.Pharmacol. 1984, 74, 417-429.

5.4 Repeated Dose Toxicity

Species:	Mouse
Strain:	Swiss Webster
Sex:	Male
Route of Administration:	Inhalation
Exposure period:	5 days
Frequency of treatment:	3 hours per day
Doses:	0.007, 0.0016, 0.0032, 0.012, 0.018, 0.023, 0.078, 0.301, 0.505, 0.82, 1.18 ppm 4 mice per group. 0.031 and 0.25 ppm for histopath.examination.
Control group:	No data specified
NOEL:	0.018 ppm
LOEL:	0.023 ppm
Method;	Other
Year:	1979
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9)

RM: Mice exposed to TDI vapour, head only. Atmospheres analysed by Marcali method.

RM: Respiratory rate measured before and after each exposure. Microscopic examination of nasal area of mice at 0.031 and 0.25 ppm.

RS: Exposures at and above 0.023 ppm produced cumulative decrease of RESPIRATORY RATE.

RS: Exposure at 0.25 ppm produced microscopic changes in NASAL MUCOSA and EPITHELIUM. No effect on nasal area at 0.031 ppm.

RE: Sangha, G.K. and Alarie, Y. Sensory irritation by toluene diisocyanate in single and repeated exposures. Toxicol.Appld.Pharmacol., 1979, 50, 533-547.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of Testing:	Salmonella typhimurium TA98, TA100, TA1535, TA1538
Concentration:	4, 20. 100, 500, 2500 µg per plate
Metabolic activation:	With
Result:	Negative
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDJ (CAS No.584-84-9), dissolved in DMSO.

RM: Assay according to Ames Test method and similar to OECD Test Guideline 471. Metabolic activation (rat liver).

RM: Positive controls: 2-nitrofluorene for TA98 and TA1538, 2-(1-chloro-2-isopropyl aminoethyl) naphthalene for TA100, TA1535. Negative control was DMSO.

RM: The criteria for judging a positive result were:

a) A 2-fold or greater increase over negative control count for any strain.

b) Negative control cultures had counts within about 50% of mean value.

c) Positive control cultures had counts greater than twice the negative control values (usually they were 10-fold greater or more).

d) A background level indicating at least 10% survival.

On this basis the test compound was judged to be non-mutagenic although numerical results were not displayed. Results for 2,4-TDI were shown only as positive or negative in tabular form for each tester strain.

RE: Anderson, D. and Styles, J.A. Appendix II. The bacterial mutation test. Br.J.Cancer, 1978, 37 924-930.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Salmonella typhimurium: TA97, TA1535
Concentration:	33-3333µg per plate (7 concentrations)
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), dissolved DMSO.

RM: Ames-type test, similar to OECD Test Guideline 471. Metabolic activation with rat or hamster liver.

RM: Positive controls, 9-aminoacridine for TA97 and sodium azide for TA1535. Negative control, DMSO.

RM: Concentrations >1000 µg TDI/plate caused precipitation.

RE: Zeiger, E., Anderson, B., Haworth, S. Lawlor, T. Mortelman, K. and Speck, W. Salmonella mutagenicity tests: III. Results from the testing of 255 Chemicals. Environ.Mutagen., 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Salmonella typhimurium: TA98, TA100
Concentration:	33-3333 µg per plate (7 concentrations)
Metabolic activation:	With and without
Result:	Positive with S9
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), dissolved in DMSO.

RM: Assay by Ames-type test, similar to OECD Test Guideline 471. Metabolic activation with rat or hamster liver preparation.

RM: Positive controls: 4-nitro-o-phenylenediamine for TA98 and sodium azide for TA100. Negative control: DMSO

RM: Chemical considered mutagenic if dose related increases in revertants were produced in replicate trials.

RM: Concentrations >1000 µg TDI per plate caused precipitation.

RM: Positive results up to 1000 µg/plates in presence of metabolic activation (rat or hamster liver) but negative in the absence of activation.

RE: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. and Speck, W. Salmonell mutagenicity tests: III. Results from the testing of 255 Chemicals. Environ.Mutagen, 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Samonella Typhimurium:TA97, TA1535
Concentration:	10-10000 µg per plate (5 concentrations)
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,6-TDI (CAS No.91-08-7), dissolved in DMSO.

RM: Ames-type test, similar to OECD Test Guideline 471. Metabolic activation with rat or hamster liver.

RM: Positive controls, 9-aminoacridine for TA97 and sodium azide for TA1535. Negative control, DMSO.

RM: Concentrations of 333 µg/plate, and greater, caused precipitation.

RE: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. and Speck, W. Salmonella mutagenicity tests: III. Results from the testing of 255 Chemicals. Environ.Mutagen, 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of Testing:	Salmonella typhimurium: TA98, TA100
Concentration:	3-666 µg per plate (6 concentrations)
Metabolic activation:	With and without
Result	Positive with S9
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,6-TDI (CAS No.91-08-7), dissolved in DMSO.

RM: Assay by Ames-type test, similar to OECD Test Guideline 471. Metabolic activation with rat or hamster liver.

RM: Positive controls: 4-nitro-o-phenylenediamine for TA98 and sodium azide for TA100. Negative control, DMSO.

RM: Chemical considered mutagenic if dose related increases in revertants were produced in replicate trials.

RM: Concentration of 333 µg TDI per plate caused precipitation.

RM: Positive results up to 333 µg/plate in presence of metabolic activator (rat or hamster liver). Negative in absence of activation.

RE: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. and Speck, W. Salmonella mutagenicity tests: III. Results from the testing of 255 Chemicals. Environ.Mutagen. 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Salmonella typhimurium TA1535, TA 1537
Concentration:	10-10000 µg per plate (5 concentrations)
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in DMSO

RM: Assay by Ames-type test, similar to OECD Test Guideline 471. Metabolic activation rat or hamster liver preparation.

RM: Positive controls: 9-aminoacridine for TA1537 and sodium azide for TA1535. Negative control: DMSO.

RM: Concentrations >1000 µg TDI/plate caused precipitation.

RE: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. and Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 Chemicals. Environ.Mutagen., 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Salmonella typhimurium TA98, TA100
Concentration:	3-1000 µg per plate (6 concentrations)
Metabolic activation:	With and without
Result:	Positive with S9
Method:	Other
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in DMSO.

RM: Assay by Ames-type test, similar to OECD Test Guideline 471. Metabolic activation with rat or hamster liver.

RM: Positive controls: 4-nitro-o-phenylenediamine for TA98, sodium azide for TA100. Negative control, DMSO.

RM: Chemical considered mutagenic if dose related increases in revertants produced in replicate trials.

RM: Positive results up to 333 µg/plate (precipitation at 1000 µg/plate), in presence of metabolic activation, but negative in absence.

RE: Zeiger, E., Andersen, B., Haworth, S., Lawlor, T., Mortelmans, K. and Speck W. Salmonella mutagenicity tests: III. Results from the test ag of 255 chemicals. Environ. Mutagen. 1987, 9, Suppl.9, 1-110.

5.5 Genetic Toxicity in Vitro

Type:	Ames test
System of testing:	Salmonella typhimurium TA1537
Concentration:	Not specified
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1980
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80-20 isomer ratio, dissolved in DMSO.

RM: Test plates placed in polyethylene bags and sealed prior to incubation.

RM: Positive control: 2,4 toluenediamine. Negative control: DMSO.

RE: Andersen, M., Binderup, M.L., Kiel, P., Larsen, H. and Maxild, J. Mutagenic action of isocyanates used in the production of polyurethanes. Scan.J.Work.Environ.Health, 1980, 6, 221-226

5.5 Genetic Toxicity in Vitro

Type:	Ames Test
System of testing:	Salmonella typhimurium TA98, TA100, TA1538
Concentration:	125, 250, 500 or 1000 µg per plate for TA98. Not specified for TA100, TA1538.
Metabolic activation:	With and without
Result:	Positive with S9
Method:	Other
Year:	1980
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in DMSO.

RM: Test plates placed in polyethylene bags and sealed prior to incubation.

RM: Positive control: 2,4 toluenediamine. Negative control: DMSO.

RM: 1000 µg TDI/plate inhibited bacterial growth.

RM: Positive results upto 500 µg TDI/plate in presence of metabolic activation (S9), negative in absence of S9.

RE: Andersen, M., Binderup, M.L., Kiel, P., Larsen, H. and Maxild, J. Mutagenic action of isocyanates used in the production of polyurethanes. Scand.J.Work.Environ.Health, 1980, 6, 221-226.

5.5 Genetic Toxicity in Vitro

Type:	Ames test
System of testing:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration:	Not specified
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4 TDI (CAS No.584-84-9)

RE: DuPont Haskell Laboratory. Bacterial mutagenicity of organoisocyanates. Report MR-2356, HL-764,76, June 7, 1978.

5.5 Genetic Toxicity in Vitro

Type:	Cytogenetic assay
System of testing:	Male human whole blood lymphocyte culture
Concentration:	0.019-0.15 µg/ml (-S9), 0.009-0.075 µg/ml (+S9)
Metabolic activation:	With and without
Result:	Ambiguous
Method:	Other - similar to OECD Test Guideline 473
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in acetone.

RM: Chromosome aberrations (CA) were analysed from 100 metaphases per treatment where possible.

RM: Positive control, cyclophosphamide. Negative control, acetone.

RM: Slight increase in CA at 0.075 and 0.15 µg/ml (-S9), not dose related. Increased CA at 0.038 µg/ml (+59), not dose related.

RM: Addition of TDI to culture medium resulted in formation of polymer-like fibres. At high doses polymer particles made metaphase analysis impossible.

RE: Maki-Paakkanen & Norppa, H. Chromosome aberrations and sister-chromatid exchanges induced by technical grade TDI and MDI in cultured human lymphocytes. Toxicol.Letters, 1987, 36, 37-43.

5.5 Genetic toxicity in Vitro

Type:	Sister-chromatid exchange assay.
System of testing:	Male human whole blood lymphocyte culture
Concentration:	0.0015-0.15 µg/ml
Metabolic activation:	With and without
Result:	Negative
Method:	Other-similar to OECD Test Guideline 479
Year:	1987
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in acetone.

RM: Sister chromatid exchanges (SCE) analysed from 50 cells per treatment, where possible.

RM: Positive control, cyclophosphamide. Negative control, acetone.

RM: Addition of TDI to culture medium resulted in formation of polymer-like fibres. At high doses, number of particles made slide reading impossible.

RE: Maki-Paakkanen & Norppa, H. Chromosome aberration and sister-chromatid exchanges induced by technical grade TDI and MDI in culture of human lymphocytes. Toxicol.Letters, 1987, 36, 37-43.

5.5 Genetic Toxicity in Vitro

Type:	Cytogenetic assay
System of testing:	Chinese hamster ovary cells
Concentration:	300-1000 µg/ml
Metabolic activation:	With and without
Result:	Negative
Method:	Other-Similar to OECD Test Guideline 473
Year:	1989
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), dissolved in DMSO.

RM: Chromosome aberrations classified as simple (breaks, fragments), complex (interchanges, rearrangements) and other (pulverised).

RM: Positive controls: MMC (-S9), cyclophosphamide (+S9). Negative control, DMSO.

RE: Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ.Molec.Mutagen., 1989, 13, 133-193.

5.5 Genetic Toxicity in Vitro

Type:	Sister chromatid exchange assay
System of testing:	Chinese hamster ovary cells
Concentration:	200-500 µg/ml (-S9), 50-500 µg/ml (+S9)
Metabolic activation:	With and without
Result:	Ambiguous
Method:	Other-Similar to OECD Test Guideline 479
Year:	1989
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9) dissolved in DMSO.

RM: 50 second-division metaphase cells were scored per dose for incidence of sister chromatid exchanges (SCE).

RM: Positive control, MMC(-S9), cyclophosphamide (+S9). Negative control, DMSO.

RM: Negative results with metabolic activation. Two out of three tests showed increased SCE, without activation.

RE: Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ.Molec.Mutagen., 1989, 13, 133-193

5.5 Genetic Toxicity in Vitro

Type:	Cytogenetic assay
System of Testing:	Chinese Hamster ovary cells
Concentration:	300-1000 µg/ml
Metabolic activation:	With and without
Result:	Positive without S9
Method:	Other, Similar to OECD Test Guideline 473
Year:	1989
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,6-TDI (CAS No.91-08-7) dissolved in DMSO.

RM: Chromosome aberrations classified as simple (breaks, fragments) complex (interchanges, rearrangements) and other (pulverised, etc.).

RM: Positive controls, MMC(-S9), cyclophosphamide (+S9). Negative control, DMSO.

RM: Significant dose related response in absence of metabolic activation (S9) but negative with S9.

RE: Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests with 27 chemicals. Environ.Molec.Mutagen., 1989, 13, 133-193.

5.5 Genetic Toxicity in Vitro

Type:	Sister chromatid exchange assay
System of testing:	Chinese hamster ovary cells
Concentration:	5-1600 µg/ml
Metabolic activation:	With and without
Result:	Ambiguous
Method:	Other-Similar to OECD Test Guideline 479
Year:	1989
GLP:	No
Test substance:	Other

R ence (RE), Remark (RM), Test substance (TS)

TS: 2,6 TDI (CAS No.91-08-7) dissolved in DMSO.

RM: 50 second-division metaphase cells scored per dose for incidence of sister chromatid exchanges (SCE)

RM: Positive control, MMC (-S9), cyclophosphamide (+S9). Negative control DMSO.

RM: Induction of SCE, in absence of S9, within concentration range 50-300 µg/ml, response not dose related. Negative in presence of S9.

RE: Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 Chemicals. Environ. Molec. Mutagen., 1989, 13, 133-193

5.5 Genetic Toxicity in Vitro

Type:	Cytogenetic assay
System of Testing:	Chinese Hamster ovary cells
Concentration:	300-1000 µg/ml
Metabolic activation:	With and without
Result:	Negative
Method:	Other, Similar to OECD Test Guideline 473
Year:	1989
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in DMSO.

RM: Chromosome aberrations classified as simple (breaks, fragments) or complex (interchanges, rearrangements).

RM: Positive controls, MMC (-S9), cyclophosphamide (+S9). Negative control, DMSO.

RE: Gulati, D.K., Witt, K., Anderson, B.. Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ.Molec.Mutagen., 1989, 13, 133-193.

5.5 Genetic Toxicity in Vitro

Type:	Sister chromatid exchange assay
System of Testing:	Chinese Hamster ovary cells
Concentration:	5-500 µg/ml
Metabolic activation:	With and without
Result:	Positive without S9
Method:	Other, Similar to OECD Test Guideline 479
Year:	1989
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in DMSO.

RM: 50 second-division metaphase cells scored per dose for incidence of sister chromatid exchange (SCE).

RM: Positive control, MMC(-S9), cyclophosphamide (+S9). Negative control, DMSO.

RM: Increased incidence of SCE at 500 µg/ml without S9. Negative in presence of S9.

RE: Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M.D. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ.Molec.Mutagen., 1989, 13, 133-193.

5.5 Genetic Toxicity in Vitro

Type:	Mammalian cell transformation assay
System of testing;	Syrian hamster kidney BHK-21 C13 cell culture
Concentration:	0.08, 0.4, 2, 10, 50, 250 µg/ml
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS 584-84-9), dissolved in DMSO.

RM: Method described by Styles (1977), see RE.

RE: Styles, J.A. Appendix III Mammalian cell transformation in vitro. Br.J.Cancer, 1978, 37, 931-936.

RE: Styles, J.A. A method for detecting carcinogenic organic chemicals using mammalian cells in culture. Br.J.Cancer 1977, 36, 558.

5.5 Genetic Toxicity in Vitro

Type:	Mammalian cell transformation assay
System of testing:	Human lung W1-38 cell culture
Concentration:	0.08, 0.4, 2, 10, 50, 250 µg/ml
Metabolic activation:	With and without
Result:	Negative
Method:	Other
Year:	1978
GLP:	No
Test substance:	Other

Reference (RE), Remark (RM), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84), dissolved in DMSO.

RM: Method described by Styles (1977), see RE.

RE: Styles, J.A., Appendix III. Mammalian cell transformation in vitro. Br.J.Cancer, 1978, 37, 931-936.

RE: Styles, J.A., A method for detecting carcinogenic organic chemicals using mammalian cells in culture. Br.J.Cancer, 1977, 36, 558.

5.6 Genetic Toxicity in Vivo

Type:	Micronucleus assay
Species:	Mouse
Strain:	C57BL
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	6 hours
Doses:	0, 11.8, 18.9 ppm (males) 0, 7.5, 11.9 ppm (females)
Method:	Other. Similar to OECD Test Guideline 474.
Year:	1992
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: 5 male, 5 female mice per group exposed to TDI for 6 hours and then bone marrow samples taken 24, 48 and 72 hours after end of exposure. Micronucleated polychromatic erythrocytes (MPE) incidence measured at each time.

RS: Small, statistically significant increase in MPE in females at 24 hours at both exposure concentrations and in males at the lower concentration.

RE: Mackay, J.M. Toluene diisocyanate: An evaluation in the mouse micronucleus test. ICI Central Toxicology Laboratory Report No.CTL/P/2616, 1992

5.6 Genetic Toxicity in Vivo

Type:	Micronucleus assay
Species:	Mouse
Strain:	C57BL
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	6 hours
Doses:	0, 5.9, 11.8, 18.9 ppm (males) 0, 3,7, 7.5, 11.9 ppm (females)
Method:	Other. Similar to OECD Test Guideline 474.
Year:	1992
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: 5 male, 5 female mice per group exposed to TDI for 6 hours and then bone marrow samples taken at 24 hours after end of exposure. Micronucleated polychromatic erythrocyte (MPE) incidence measured at each time.

RS: Exposure levels of 11.8ppm in males and 11.9 ppm in females were lethal. Therefore bone marrows assessed only at 5.9 ppm in males and 3.7, 7.5 ppm in females.

RS: No effect on male bone marrow at 5.9 ppm. Small statistically significant increase in MPE in females at 3.7 and 7.5 ppm. However, values within control range. Changes not considered to be biologically significant.

RM: Positive control, vinyl chloride, induced statistically and biologically significant increases in MPE, demonstrating sensitivity of test system.

RE: Mackay, J.M. Toluene diisocyanate: An evaluation in the mouse micronucleus test, ICI Central Toxicology Laboratory Report No.CTL/P/2616, 1992.

5.6 Genetic Toxicity in Vivo

Type:	Micronucleus assay
Species:	Mouse
Strain:	CD-1
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	6 hours per day, 5 days per week, for 4 weeks
Doses:	0, 0.05, 0.15 ppm. 5 males, 5 females per group
Method:	Other
Year:	1985
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

RM: Mice, 5-6 weeks old, exposed to TDI vapour.

RM: Bone marrow from femur aspirated with 10% foetal calf serum, suspension centrifuged and film of sedimented cells prepared. Film stained and number of micronuclei-containing cells per 1000 polychromatic erythrocytes estimated.

RS: No dose or treatment related percentage increase in micronucleated erythrocytes.

RE: Owen, P.E. The toxicity and carcinogenicity of TDI vapour when administered to mice over a period of approximately 2 years. Hazleton Laboratories Europe Ltd. Report No.2519-484/2, March 1986.

Also published in -

Loeser, E. Long-term toxicity and carcinogenicity studies with 2,4/2,6-TDI (80/20) in rats and mice. Toxicol.Letters, 1983, 15, 71-81.

5.6 Genetic Toxicity in Vivo

Type:	Micronucleus assay
Species:	Rat
Strain:	Sprague-Dawley
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	6 hours per day, 5 days per week, for 4 weeks
Doses:	0, 0.05, 0.15 ppm. 5 males, 5 females per group
Method:	Other
Year:	1980
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

RM: Rats, 5-9 weeks old, exposed to TDI vapour.

RM: Bone marrow from femur aspirated with 10% foetal calf serum, suspension centrifuged and film of sedimented cells prepared. Film stained and number of micronuclei - containing cells per 1000 polychromatic erythrocytes estimated.

RS: Slight increase in micronucleated erythrocytes in males and females at both dose levels. However, statistically significant at lower level only; therefore result not considered to be biologically significant.

RE: Owen, PE. The toxicity and carcinogenicity to rats of TDI vapour administered by inhalation for a period of 113 weeks. Hazleton Laboratories Europe Ltd. Report No. 2507-484/1, Oct 1980.

RE: Loeser, E. Long-term toxicity and carcinogenicity studies with 2,4/2,6 TDI (80/20) in rats and mice. Toxicol.Letters, 1983, 15, 71-81.

5.6 Genetic Toxicity in Vivo

Type:	Unscheduled DNA synthesis
Species:	Rat
Strain:	Fischer 344
Sex:	Male
Route of administration:	Inhalation
Exposure period:	4 hours
Doses:	0, 0.077, 0.40, 1.49 ppm, 4 rat/group
Method:	Other
Year:	1988
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

RM: Rats exposed to TDI vapour and hepatocyte and lung cultures prepared from the tissues 12 hours after the end of exposure. Cultures were transferred to glass slides which were then exposed to autoradiography, stained with H & E and scored for assessment.

RM: 2,4-toluenediamine (TDA) used as positive control, either by inhalation at 0.11 ppm or by gavage at 150 mg/kg.

RS: Rats at top dose of 1.49 ppm TDI showed slow irregular breathing, piloerection, eye and nose irritation. No effect at lower levels.

RS: TDI did not induce unscheduled DNA synthesis in lung or hepatocytes at any of the exposure levels. TDA (positive control) did not induce UDS by inhalation at 0.11 ppm but did by oral administration.

RE: Benford, D.J. and Riley,R.A. Mutagenicity study for the detection of unscheduled DNA synthesis ex-vivo in hepatocytes and lung following a single exposure of TDI to rats by inhalation. Study No.T0024338. Bayer AG Report No.R4465, 15.6.88.

5.7 Carcinogenicity

Species:	Rat
Strain:	Fischer 344
Sex:	Male/female
Route of administration:	Gavage
Exposure period:	106 weeks
Frequency of treatment:	5 days per week
Doses:	0, 30, 60 mg/kg males; 0, 60, 120 mg/kg females. (N.B. these are nominal values values, see RM).
Control group:	Yes concurrent vehicle
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Groups of 50 male, 50 female rats dosed by gavage, TDI in corn oil. The corn oil contained 0.05% water. Regular analysis of TDI corn oil solutions throughout study showed estimated doses to be 23 and 49 mg/kg for males and 49 and 108 mg/kg for females.

RM: Rats were housed 5 males or 5 females per cage. Animals observed twice a day. Bodyweights measured weekly for 1st 13 weeks, then monthly. All rats, except those found dead with advanced autolysis, given gross examination. Histopathological examination on 35+ tissues from each rat.

RM: Tumour incidence statistically analyzed by methods of Peto et al (1980). Fisher exact test for pairwise comparisons and Cochran-Armitage linear trend test.

RS: No clinical signs due to treatment. Dose-related DEPRESSION OF BODYWEIGHT GAIN, commencing at week 10 in males and week 20 in females.

RS: INCREASED MORTALITY in treated groups, compared to controls, seen early in study and was pronounced throughout, e.g. 1/50, 15/50, 18/50 in control, low and high dose male groups, at 52 weeks, and 14/50, 32/50, 40/50 at 104 weeks.

RS: ACUTE BRONCHOPNEUMONIA found in increased incidence in dosed groups,2/50, 6/50, 14/50, control, low and high dose males; 1/50, 10/50, 25/49 in females.

Continued.....

RS: Because of early mortality in dosed groups the tumour incidences had to be adjusted in statistical analyses to allow for this. Also, comparisons made with historical controls. The following tissues were considered to show increased tumour incidences due to treatment:
SUBCUTANEOUS TISSUE, increase FIBROMA plus FIBROSARCOMA in males at 30 and 60 mg/kg, and in females at 120 mg/kg.
MAMMARY GLAND TUMOURS in females at 60 and 120 mg/kg.
PANCREATIC ACINAR CELL ADENOMA in males at 30 and 60 mg/kg and ISLET CELL TUMOURS at 60mg/kg. ISLET CELL ADENOMA in females at 60 and 120 mg/kg.
LIVER NEOPLASTIC NODULES in females at 60 and 120 mg/kg.

RM: About 50% of tumours were found in rats at termination, remainder in animals dying between weeks 77 and 108.

RM: It was noted that 2,4-toluenediamine, the hydrolysis product of 2,4-TDI, gave rise to induction of similar tumours in rats in gavage studies.

RM: The TDI study has been criticized for exceeding maximum tolerated dose, irregularities with gavage technique, compound storage and analysis, and for using a route of exposure inappropriate for assessing occupational risk in humans (Ader et al 1987, see RE).

RE: National Toxicology Program. NTP technical report on the toxicology and carcinogenesis studies of commercial grade 2,4 (80%)- and 2,6 (20%)-toluene diisocyanate (CAS No.26471-62-5) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, North Carolina, US Dept. Health & Human Services, Public Health Service, National Institutes of Health NTP TR251, NIH Publication No.86-2507, August 1986.
Also published as:
Dieter, M.P., Boorman, G.A., Jameson, C.W., Matthews, H.B. and Huff, J.E. The carcinogenic activity of commercial grade TDI in rats and mice in relation to the metabolism of the 2,4- and 2,6-TDI isomers. Toxicol.Ind.Health, 1990 6, 599-621.

RE: Ader, A.W., Carney, I.F. and Loeser, E. Risk evaluation of chronic exposure to TDI based on long-term animal studies. Proc.SPI/FSK Polyurethanes World Congress 1987, 188-192.

5.7 Carcinogenicity

Species:	Mouse
Strain:	B6C3F1
Sex:	Male/female
Route of administration:	Gavage
Exposure period:	105 weeks
Frequency of treatment:	5 days per week
Doses:	0, 120, 240 mg/kg, males; 0, 60, 120 mg/kg, females (N.B. these are nominal values, see RM).
Control group:	Yes concurrent vehicle
Method:	Other
Year:	1986
GLP:	No
Test substance:	Other

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Groups of 50 male, 50 female mice, dosed, by gavage, TDI in corn oil. The corn oil contained 0.05% water. Regular analyses of TDI corn oil solutions throughout study showed estimated doses to be 108 and 202 mg/kg for males and 49 and 108 mg/kg for females.

RM: Mice were housed 5 males or 5 females per cage. Animals were observed twice a day. Bodyweights measured weekly for 1st 13 weeks then monthly. All mice, except those found dead with advanced autolysis, given gross examination. Histopathological examination on 35+ tissues from each rat.

RM: Tumour incidence statistically analysed by methods of Peto et al (1980), Fisher exact test for pairwise comparisons and Cochran-Armitage linear trend test.

RS: No clinical signs due to treatment. Dose-related DEPRESSIONS IN BODYWEIGHT GAIN in males, slight depression at top dose only in females.

RS: INCREASED MORTALITY in treated male groups, apparent early in the study. At 52 weeks incidences were 0/50, 4/50 and 10/50 in control, low and high dose and 4/50, 10/50, 21/50 at 104 weeks. Females affected at top dose.

RS: Increased incidence of KIDNEY CYTOMEGALY in tubules near corticomedullary junction in males, 0/50, 45/48, 41/50, control, low and high dose.

Continued.....

RS: Following tissues considered to show increased tumour incidence due to treatment: CIRCULATORY SYSTEM, slight increase in HEMANGIOMA plus HEMANGIOSARCOMA in females at 120 mg/kg.

LIVER, increased incidence in HEPATOCELLULAR ADENOMA in females at 120 mg/kg.

RM: It was noted that 2,4-toluenediamine, the hydrolysis product of 2,4-TDI, gave induction of similar tumours in mice in gavage studies.

RM: The TDI study has been criticized for exceeding maximum tolerated dose, irregularities with gavage technique, compound storage and analysis and for using route of exposure inappropriate for assessing human occupational exposure (Ader et al 1987 see RE).

RE: National Toxicology Program. NTP technical report on the toxicology and carcinogenesis studies of commercial grade 2,4 (80%)- and 2,6 (20%)-toluene diisocyanate (CAS No.26471-62-5) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, North Carolina, US Dept. Health & Human Services, Public Health Service, National Institutes of Health NTP TR251, NIH Publication No.86-2507, August 1986.
Also published as:
Dieter, M.P., Boorman, G.A., Jameson, C.W., Matthews, H.B. and Huff, J.E. The carcinogenic activity of commercial grade TDI in rats and mice in relation to the metabolism of the 2,4- and 2,6-TDI isomers. Toxicol.Ind.Health, 1990 6, 599-621.

RE: Ader, A.W., Carney, I.F. and Loeser, E. Risk evaluation of chronic exposure to TDI based on long-term animal studies. Proc.SPI/FSK Polyurethanes World Congress 1987, 188-192.

5.7 Carcinogenicity

Species:	Rat
Strain:	Sprague-Dawley
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	113 weeks
Frequency of treatment:	6 hours per day, 5 days per week
Doses:	0,0.05, 0.15 ppm
Control group:	Yes concurrent vehicle
Method:	Other. Similar to OECD Test Guideline 453
Year:	1980
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

RM: Groups of 126 male, 126 female rats exposed to TDI vapour. Animals housed 6 males or 6 females per cage and exposed in 9m³ chambers. Rat approx. 8-9 weeks old at start of exposure. Atmospheres monitored at least 5 times each day by two methods: Marcali test and test paper monitor.

RM: Rats observed twice daily, before and after exposure. Bodyweight measured weekly for 1st 8 weeks, then monthly. Haematology, blood and urine biochemistry on 7 males, 7 females, at 6, 12, 18 months and termination. Haematology: Hb, RBC, PCV, WBC.
Blood biochem = BUN, AlkP and GPT.
Interim sacrifices on 7 males, 7 females at 6, 12 and 18 months.
Gross examination on all rats dying and at scheduled kills.
Organ weights - brain, liver, heart, gonads, kidney.
Histopathology - on 35+ tissues from each rat.

RS: No treatment related effect on mortality. Mortality incidences at termination 65%, 67%, 71% in males and 67%, 75% and 64% in females for control, low and high dose respectively.
No treatment related changes for clinical signs.

RS: BODYWEIGHT GAIN REDUCED for high dose males and females over 1st 12 weeks. This persisted but did not worsen over the remaining period of the study (<10% below control value for males, approx, 10-15% for females).

RS: No effect on haematology, blood or urine biochemistry or organ weights.

Continued...

RS: Treatment related INCREASED INCIDENCE of RHINITIS in the anterior portion of the nasal cavity of rats exposed to TDI. Minimal grade rhinitis was present in control males (41% of animals) and females (24%). Incidence and severity was not increased in low dose males but was increased in high dose and in both exposed groups of females. Response considered to be due to local irritation. (Subject of separate report, see RE).

RM: No evidence for any treatment related increased in tumour incidences.

RE: Owen, P.E. The toxicity and carcinogenicity to rats of TDI vapour administered by inhalation for a period of 113 weeks. Hazleton Laboratories Europe Ltd. Report No.2507-484/1, October 1980.
Also published as a scientific paper:
Loeser, E. Long-term toxicity and carcinogenicity studies with 2,4/2,6-TDI (80/20) in rats and mice. Toxicol.Letters, 1983, 15 71-81.

RE: Glaister, J.R., Addendum Section No.1 Histopathology of the nasal cavity. Hazleton Laboratories Europe Ltd., Report No.2507-484/1 March 1984.

5.7 Carcinogenicity

Species:	Mouse
Strain:	CD-1
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	104 weeks
Frequency of treatment:	6 hours per day, 5 days per week
Doses:	0, 0.05, 0.15 ppm
Control group:	Yes concurrent vehicle
Method:	Other. Similar to OECD Test Guideline 453
Year:	1986
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

RM: Groups of 120 male, 120 female mice exposed to TDI vapour. Animals caged individually and exposed in 5.5m³ chambers. Mice approx. 5-6 weeks old at start of exposure. Atmospheres monitored continuously by Test Paper monitors and checked by Marcali method at regular intervals.

RM: Mice observed twice daily, before and after exposure. Bodyweights measured weekly for 1st 8 weeks and then every 2 weeks. Haematology, blood and urine biochemistry on 10 males, 10 females at 26, 52, 78 weeks. Haematol = Hb, RBC, PCV, WBC. Blood biochem = GPT, AlkP, glucose, urea, proteins. Interim sacrifices, 10 males, 10 females at 26, 52 and 78 weeks. Gross examination on all rats dying and at scheduled kills. Organ weights - brain, liver, kidney, heart, lungs, testes Histopathology - 35+ tissues from each mouse.

RS: No effect on male mortality. Females showed INCREASED MORTALITY at top level and at lower level as study progressed. Incidence at termination in control, low and high dose; 75, 66, 66 in males, 60, 73, 72 in females. Increased clinical signs of swollen abdomens and opaque watery eyes, probably treatment related, seen from week 65 onwards.

RS: BODYWEIGHT GAIN REDUCED in high dose males and females.

RS: No effect on haematology, blood or urine biochemistry or organ weights.

Continued...

RS: Dose-related increase in CHRONIC or NECROTIC RHINITIS incidence and severity. Highest grade of severity was associated with morbidity and mortality in a proportion of mice. Lesions of variable incidence and severity also in lower respiratory tract of some mice with a higher incidence at 0.15 ppm. These included INTERSTITIAL PNEUMONITIS, CATARRHAL BRONCHITIS and BRONCHIOLITIS.

RS: No evidence for any treatment related increases in tumour incidence.

RE: Owen, P.E. The toxicity and carcinogenicity of TDI vapour when administered to mice over a period of approxidmately 2 years. Hazleton Laboratories Europe Ltd. Report No.2519-484/2, March, 1986.
Also published as a scientific paper:
Loeser, E. Long-term toxicity and carcinogenicity studies with 2,4/2,6-TDI (80/20) in rats and mice. Toxicol.Letters, 1983, 15, 71-81.

5.8 Toxicity to Reproduction

Type:	Two generation Study
Species:	Rat
Strain:	Sprague-Dawley
Sex:	Male/female
Route of administration:	Inhalation
Exposure period:	Days 0-19 of gestation (both generations)
Frequency of treatment:	6 hours per day, 7 days per week
Premating exposure period:	10 weeks at 6 hours per day, 5 days per week for F_o and 12 weeks for F_1, at same frequency.
Duration of the test:	See RM for detail
Doses:	0, 0.02, 0.08, 0.30 ppm. 28 males, 28 females per group
Control group:	Yes concurrent vehicle
NOEL Parental:	<0.02 ppm males 0.08 ppm females
NOEL F1 Offspring:	0.30 ppm
NOEL F2 Offspring:	0.02 ppm
Method:	Other. Similar to OECD Test Guideline 416
Year:	1989
GLP:	Yes
Test substance:	As prescribed by 1.1-1.4

Reference (RE). Remark (RM), Result (RS), Test substance (TS)

RM: Rats exposed to TDI vapour in 4320 litre chambers. Atmospheres monitored by paper tape devices based upon modified Marcali method.

RM: Methodology conformed to OECD Test Guideline 416.

RM: F_o parents exposed 6h/day, 5 days/week for 10 weeks, and then, during mating, 6h/day, 7 days/week until day 19 of gestation. Dams not exposed day 20-24; then exposed again 6h/day, 7 days/week to day 20 postnatal. At day 21 litters weaned. Parents for second generation selected and exposed 6h/day, 5 days/week for 12 weeks prior to mating. Exposure during mating and subsequently, as above.

RM: Mating, 1 male to 1 female.

RM: Parents observed twice daily and weighed weekly pre-mating. Mated females weighed on days 0, 7, 14 and 21 of gestation, and postnatal days 1, 4, 7, 14 and 21.

Continued...

RM: Pups examined and sexed at birth. Survival recorded at 0, 4, 7, 14 days and at weaning. Pups sexed and weighed at 1, 4, 7, 14 days and at weaning. All pups examined for abnormalities.

RM: All parents given gross examination and 10 males, 10 females at top exposure level and in controls examined histopathologically.

RS: F_0 males showed increased NASAL DISCHARGE at 0.3 ppm in pre-mating exposure period.
F_1 females showed NASAL CRUSTATION at 0.3 ppm and males showed REDUCED BODYWEIGHT GAIN at this level, pre-mating.

RS: F_0 males and females showed treatment related increase in RHINITIS and ALTERATION OF RESPIRATORY EPITHELIUM in NASAL TURBINATES at 0.3 ppm. Increased RHINITIS also at 0.08 ppm.
F_1 males and females showed increased RHINITIS at 0.08 and 0.3 ppm, with males affected also at 0.02 ppm.

RS: F_2 pup BODDYWEIGHT REDUCED, up to day 21, at 0.08 and 0.3 ppm.

RS: NO EFFECT ON REPRODUCTIVE INDICES at levels tested.

RE: Tyl RW and Neeper-Bradley TL. Two-generation reproduction study of inhaled TDI in CD (Sprague-Dawley)rats. Bushey Run Research Centre, Project Report 51-576, March 17, 1989.

5.9 Developmental Toxicity/Teratogenicity

Species	Rat
Strain	Sprague-Dawley
Sex	Female
Route of Administration	Inhalation
Duration of the test	21 days (days 0-21 of gestation)
Exposure Period	Days 6-15 of gestation
Frequency of treatment	6 hours per day
Doses	0, 0.02, 0.10, 0.50ppm. 25 females per group
Control Group	Yes concurrent vehicle
NOEL Maternal toxicity	0.1ppm
NOEL teratogenicity	0.5ppm
Method	Other-Similar to OECD Test Guideline 414
Year	1988
GLP	Yes
Test substance	As prescribed by 1.1 - 1.4

Freetext - Reference (RE), Remark (RM), Result (RE), Test substance (TS)

RM: Pregnant rats exposed to TDI vapour in 4320 litre chambers. Atmospheres monitord by Marcali method.

RM: Overall methods conform to OECD Test Guideline 414, except maternal bodyweight measured more frequently at gestation days 0, 6, 9, 12, 16 and 21.

RS: No mortality in dams, no abortions or early deliveries. Respiratory noise in 0.5ppm animals.

RS. Maternal bodyweight gain significantly depressed over the exposure period at 0.5ppm.

RS: No effect on pregnancy rate, number of corpora lutea, number of viable implants, no live foetuses, or sex ratio. Foetal bodyweight not affected.

RS: No effect on incidence of external, visceral or skeletal malformations.

RS: Increased incidence of POORLY OSSIFIED CERVICAL CENTRUM 5, indicating minimal foetoxicity, at 0.5ppm.

RS: No effect level for maternal and developmental toxicity is 0.1ppm.

RS: TDI NOT TERATOGENIC at levels tested.

RE: Tyl RW. Developmental toxicity study of inhaled TDI vapor in CD (Sprague-Dawley) rats. Bushy Run Research Center, Revised Project Report 50-592, Nov 8, 1988.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-TDI (84% 2,4-, 16% 2,6-).

RM: Male & female Sprague-Dawley rats, 150-200g bwt given single doses intramuscularly, 38m Ci/mM ^{14}C-TDI. Doses = 17-32 µg TDI per rat.

RM: Blood sampled at regular intervals after injection. Animals placed in glass metabolism cages for collection of urine/faeces/CO_2. Rats killed and homogonised at termination. ^{14}C measured in all samples.

RS: Blood ^{14}C peaked at approx 24 hours. Elimination from blood followed two phase pattern. $T_{\frac{1}{2}}$ for diffusion from muscle, approx 30 min.

RS: Urinary excretion 53%, faecal 39%, expired air negligible, carcass 4%, all after 360 hours.

RM: This was a preliminary study to an investigation of uptake, distribution and excretion via inhalation.

RE: Laboratoire d'Etudes du Metabolisme des Medicaments, A Study of the diffusion rate of TDI in rats contaminated via the respiratory system. Preliminary Study. Cen-Saclay, 1976.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-TDI (84% 2,4-, 16% 2,6-)

RM: 12 rats exposed to ^{14}C-TDI by inhalation.

RS: Elimination of ^{14}C from blood is in 2 phases, 90% of radioactivity in plasma is associated with proteins.
86% of dose eliminated in 5 days.
8% in bile during 1st 52 hours.
Faecal excretion > urinary excretion.
^{14}C distributed uniformly throughout body.

RS: Proportion of polar derivatives in urine, decreases with time; less polar increase. Most abundant derivative accounts for 25-30% of ^{14}C in urine.

RE: Laboratoire D'Etudes du Metabolisme des Medicaments, A Study of the diffusion rate of TDI in rats contaminated via the respiratory tract. CEN-SACLAY (undated abstract).

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-TDI, 80:20 isomer ratio, dissolved in corn oil.

RM: Fischer 344 male rats, 7-9 weeks old, given single oral dose TDI at 6 or 60 mg/kg by gavage. Animals placed individually in glass metabolism chambers and urine faeces and expired air collected for periods up to 96 hours. Blood and tissue samples also taken. Radioactivity measured in all samples. Urine, faeces, GI contents and liver also analysed by HPLC.

RS: Activity appeared in blood within 30 min, peaked at 1-2h and then decreased slowly. 1% of dose at low dose and 0.5% at high. Excretion of radioactivity from urine, most rapid 0-6 hours, decreasing rapidly by 24h. 23% of dose excreted at low dose, 16% at high.
76-81% excreted in faeces, mainly 6-48 hours. Negligible amount of activity in expired air. Low activity in tissues, with highest amounts in blood, liver, kidney.

RS: Complex metabolic profile, no attempt at identification.

RE: Stoltz M, Czarnecki D, Litle L, Pallas F and El-Hawari M. Metabolism and disposition of ^{14}C-labelled TDI following oral and inhalation exposure: preliminary studies. Mid west Research Institute, MRI Project No.8072-A, Kansas City, June 12, 1987.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-TDI, 80:20 isomer ratio.

RM: Fisher 344 male rats, 7-9 weeks old, exposed to TDI vapour, head only, at 0.6 or 2.0ppm for 4 hours. Animals placed in individual glass metabolism chambers and urine, faeces, expired air, blood and tissue samples taken at times up to 96h. Radioactivity measured in all samples. Urine, faeces, GI content and liver also examined by HPLC.

RS: 4% of radioactivity in blood immediately after low exposure, falling to 2% 24h later. 2% and 1% respectively for higher exposure. Urinary excretion most rapid over 0-6h, still continuing at 96h. Total excretions at this time were 24% for low, and 20% for high exposure.
Faecal excretion about 53-54% in 96h.
Tissue activity generally low but blood, liver, kidney nasal area and lungs contained highest levels.

RS: Complex metabolic profile, no attempt at identification.

RE: Stoltz M, Czarnecki D, Litle L, Pallas F., and El-Hawari M. Metabolism and disposition of ^{14}C-labelled TDI following oral and inhalation exposure: preliminary studies. Midwest Research Institute, MRI Project No.8072-A, Kansas City, June 12, 1987.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,6 TDI (CAS No.91-08-7) in DMSO

RM: Aliquot of ^{4}C-TDI solution added to rat stomach contents homogenate or to rat serum and incubated at 37°C for up to 30 min. Reactions stopped at intervals by addition of piperidine, then centrifuged and analysed by HPLC.
% 2,6-TDI remaining determined.

RS: Rapid rates of reaction - in stomach contents, only 4% TDI remained after 10 min and in serum only 10% remained after 1 min.

RE: Jeffcoat A.R, Disposition of 2,6-TDI in Fischer 344 rats. Research Triangle Institute Project Report No.7, North Carolina, July 1985

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,6-TDI (CAS No.91-08-7) in pure dry corn oil.

RM: Fischer 344 male rats given single oral dose at 60 or 900 mg/kg, 7 rats per group. Animals placed, individually, in glass metabolism chambers and urine, faeces and expired air collected over 72h. Then rats killed and blood and selected tissues taken. Radioactivity measured in all samples. Urine also anlaysed by HPLC.

RS: At 900 mg/kg, rats had distended blood filled stomachs and empty intestines. White polymer material on stomach wall.

RS: ^{14}C-urinary excretion 5% at 900mg/kg, 12% at 60 mg/kg. Half at 60mg/mg was 2,6-bis (acetylamino) toluene. ^{14}C-faecal excretion 20-50% at 900mg/kg, 55-65% at 60mg/kg. ^{14}C-tissue concentrations highest in blood, liver, kidney and stomach at 900mg/kg and in blood and kidney at 60mg/kg.

RM: Suggested that at lower doses 2,6-TDI hydrolysed in stomach then absorbed and acetylated prior to urinary excretion.

RE: Jeffcoat A.R. Disposition of 2,6-TDI in Fischer 344 rats. Research Triangle Institute Project Report No.7, North Carolina July 1985.

5.10 Other Relevant information

Type: Metabolism

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,4-TDI (CAS No.584-84-9) dissolved in pure dry corn oil

RM: Two groups of male Fischer 344 rats dosed 60mg/kg TDI orally by gavage. One group (3 rats) housed in glass metabolism cages and urine, faeces, expired air collected over 48h. Other group (4 rats) killed 2h after dosing and tissues collected. All samples measured for radioactivity.

RM: Metabolic profiling and identification by HPLC, urine and faeces, urine also extracted, derivatised and analysed by GC/MS

RS: [illegible] % of ^{14}C-dose in urine, faeces, tissues and carcass 48h after dosing. 81% in faeces, 8% in urine 4% tissues (highest in GIT). Urinary excretion half-life = 7.5h. Expired air ^{14}C, negligible.

RS: 65% of quantitated urinary metabolites were acid-labile conjugates. Free TDA and its mono - and diacetyl derivatives present in urine.

RM: Urine and faecal HPLC profiles same as those from inhalation exposure.

RE: Timchalk C, Smith F.A. and Bartels M.J, Metabolic fate of ^{14}C-2,4-TDI in Fishcer 344 rats. The Dow Chemical Co., Midland. Study ID K-022862-003 January 9, 1992.

5.10 Other Relevant information

Type: Metabolism

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,4-TDI (CAS No.584-84-9).

RM: Two groups of male Fischer 344 rats were exposed, head only, for 4h to 2ppm ^{14}C-TDI vapour. Following exposure, one group (4 rats) was placed in glass metabolism cages, while the other group (4 rats) were killed. Urine, faeces, blood and tissues collected up to 48h. All samples measured for radioactivity.

RM: Metabolic profiling and identification by HPLC, urine and faeces. Urine also extracted, derivatised and analysed by GC/MS.

RS: Over 48h, 15% ^{14}C in urine, 47% in faeces, 34% in tissues and carcass. Highest tissue activity in lungs. Urinary excretion half-life = 20h.

RS: 90% of quantified urinary metabolites were acid-labile conjugates. Free TDA not detected in urine. Its mono- and diacetyl derivatives were present.

RM: Urine and faecal HPLC profiles same as those from oral dosing.

RE: Timchalk C, Smith F.A. and Bartels M.J. Metabolic fate of ^{14}C-2,4-TDI in Fisher 344 rats. The Dow Chemical Co., Midland. Study ID K-022862-003 January 9, 1992.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), test substance (TS)

TS: ^{14}C-2,4-TDI (CAS No.584-84-9).

RM: Male Fischer 344 rats, 4 per group, given ^{14}C-TDI at 60mg/kg by gavage in pure dry corn oil, or exposed to 2ppm as vapour, head only, for 4 hours. Rats killed 2h after oral dose or immediately post-inhalation exposure. 200µl blood samples taken for radioactivity measurement. Plasma separated and submitted to molecular sieve fractionation and radioactive assay. Plasma retentate subjected to gel electrophoresis.

RS: ^{14}C in bloodstream was at comparable levels after either gavage or inhalation administration. In each case, majority of radioactivity in plasma was in a conjugated form. The predominant conjugate after inhalation had relative molecular wt of 70k Da. Less found after oral dose and correspondingly more low mol. wt. products present. TDA may be a predominant product in the low mol.wt.products.

RE: Kennedy A.L, Timchalk C. and Brown W.E. Analysis of the differential reactivity of isocyanates: Effect of exposure method. Poster presented at the conference on Measuring, Understanding and Predicting Exposures in the 21st Century, November 18-21, 1991, Atlanta, Georgia.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,4-TDI (CAS No.584-84-9)

RM: 7 groups of male Hartley guinea pigs, 300-400g b.wt, exposed to ^{14}C-TDI vapour at concentrations 0.0005-0.146ppm for periods of 1-5 hours. Animals exposed individually in whole body plethysmographs, 4 per group.

RM: Carotid arteries cannulated prior to exposure and blood samples taken at frequent intervals during exposure. Blood, bile, urine and tissue samples taken at intervals after exposure. Radioactivity measured in all samples.

RS: Uptake of radioactivity in blood shown to be linear for all exposure concentrations and periods.

Blood activity continued to increase for about 2h post-exposure, followed by a slow decline, but ^{14}C-levels persisted after 2 weeks. Highest activity in urine and bile immediately post exposure, followed by significant decline by 72h post-exposure. Tissues showing highest levels of activity were trachea and lungs. Small amounts in kidney, liver, heart. Tissue activity persisted up to 2 weeks.

RE: Kennedy A.L, Stock M.F, Alarie Y. and Brown W.E. Uptake and distribution of ^{14}C during and following exposure to radioactive TDI. Toxicol.Appld.Pharmacol, 1989, 100, 280-292.

5.10 Other Relevant Information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: ^{14}C-2,4-TDI (CAS No.584-84-9)

RM: Groups of male Fischer 344 rats (150-200g) exposed head only to ^{14}C-TDI at atmospheric concentrations of 0.026, 0.143 or 0.82 ppm, 4 rats/group, for 4 hours.

RM: Immediately after exposure, blood collected and trachea, lung, oesophagus, stomach, kidneys, adrenal glands, heart, spleen and liver taken for ^{14}C measurement.

RM: Blood separated into plasma/cells for ^{14}C measurement. Plasma submitted to molecular sieve fractionation; retentate subjected to gel electrophoresis.

RS: Highest levels readioactivity associated with airway tissues at all exposure concentrations. % ^{14}C in blood ranged from 10-13% at 0.026 ppm, 6.5-7.6% at 0.143 ppm, 4.7-6.8% at 0.82 ppm. Uptake was linear at all exposure concentrations.

RS: Majority of ^{14}C in blood was in plasma. Most (95-98%) was associated with conjugated products > 10k Da. Gel electrophoresis showed this was mostly associated with 70k Da protein.

RM: Above results compared with those for guinea pig (Kennedy et al 1989). Uptake and distribution is similar in both species at similar exposure concentrations. Highest specific activity was in respiratory tract, with rat showing higher level of labelling.

RE: Kennedy A.L, Wilson T.R., Stock M.F., Alarie Y. and Brown W.E., Interspecies comparison of uptake and distribution of radioactivity following inhalation exposure to ^{14}C- labelled TDI. Draft paper for publication 1993.

RE: Kennedy A.L., Stock M.F., Alarie Y. & Brown W.E. Uptake and distribution of ^{14}C during and following exposure to radioactive TDI. Toxicol Appld Pharmacol, 1989, 280-292.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Two guinea pigs exposed to 1ppm TDI, by inhalation, for 3h/day for 5 days; then, together with unexposed animals, challenged with 0.1/ppm ^{14}C-TDI.

RS: Serum contained radioactivity associated with 77k Da protein in TDI animals.

RS: Histopathological examination of respiratory tissue showed epithelial cell loss due to TDI exposure. Autoradiography showed that the ^{14}C label penetrated along the respiratory tree as far as terminal bronchioles.

RE: Kennedy A.L, Singh G. and Brown W.E. A histologic analysis of the respiratory tract following inhalation of radioactively labelled TDI. FASEB Abstract April 1987.

5.10 Other Relevant information

Type: Toxicokinetics

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Guinea pigs exposed to 1ppm TDI, by inhalation, 3h/day for 5 days. These and control animals challenged with 0.1ppm ^{14}C-TDI for 3h, 25 days after initial exposure.

RS: Serum taken 21 days after initial exposure contained antibodies to TDI. ^{14}C appeared in bloodstream of TDI sensitised animals 5 times faster than controls. ^{14}C was found mainly in plasma.

RE: Hill B.L, Karol M.H. and Brown W.E. The fate of inhaled ^{14}C-TDI in sensitised guinea pigs. Toxicologist, 1986, 6, 15.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio.

RM: Female guinea pigs, 4 per group, exposed to TDI vapour at 0.25ppm, 3 hours per day for 5 days, (4 groups). Respiratory rate measured during study, blood serum, obtained prior to exposure and at time intervals after exposures, evaluated for TDI - specific antibodies.

RS: Respiratory rate decreased by 50% in 1st hour 1st exposure, then to 30% in 2nd hour. It fell again to 20-30% after subsequent exposures.

RS: TDI - specific antibodies found in 6/16 animals, one with IgE activity.

RS: Animals re-exposed to 0.02ppm TDI for 30 min and respiratory rate measured again. Only small decrease during exposure, recovery within 2 hours.

RM: Pulmonary hypersensitivity not demonstrated.

RE: Karol MH, Dixon C, Brady M and Alarie Y. Immunologic sensitization and pulmonary hypersensitivity by repeated inhalation of aormatic isocyanates. Toxicol.Appld.Pharmacol, 1980, 53, 260-270.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80: 20 isomer ratio.

RM: 3 groups of 4 female guinea pigs sensitised by topical application of TDI, neat or in olive oil, to shaved dorsal areas. Groups received i) 50 µl 25% TDI, ii) 50µl TDI or iii) 2 x 50 µl TDI. Two weeks later animals challenged by exposure to 0.005ppm TDI vapour and respiratory rate measured.

RS: i) 1/4 animal responded with 49% increase in respiratory rate.
ii) None responded.
iii) 2/4 animals responded with 44% and 61% increase in respiratory rate.

RM: Study indicates that skin contact to TDI can result in pulmonary hypersensitivity

RE: Karol M.H, Hauth B.A, Riley E.J and Magreni C.M. Dermal contact with TDI produces respiratory tract hypersensitivity in guinea pigs. Toxicol.Appl.Pharmacol, 1981 58, 221-230.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80 : 20 isomer ratio

RM: Groups of female guinea pigs exposed by inhalation head only, to TDI vapour at concentrations 0.12-10 ppm, 3h per day for 5 days. Evaluated at day 22 for TDI-specific antibodies, skin and pulmonary reactivity.

RM: Another group of animals exposed to 0.02 ppm TDI, via whole body exposure, 6 hours per day, 5 days/week for a total of 70 exposures, together with a concurrent control group. TDI-antibodies etc, measured as above.

RS: Respiratory rate decreased in exposure concentration dependent manner over range 0.12-0.93 ppm. At day 22, no antibodies detected in serum at 0.12 ppm, low titre in 5/12 animals at 0.36 ppm and increased titres with increasing concentrations up to 0.93 ppm where all animals affected.
Bronchial provocation with antigen conjugates showed pulmonary sensitivity at 0.36-0.93 ppm but not at higher concentrations of TDI.
Dermal sensitivity, as evaluated by id injection of antigen solution, was shown by erythema in groups exposed to 0.12-7.6 ppm TDI.

RS: Exposure to 0.02 ppm TDI over 4 months did not produce an antibody response, dermal or pulmonary sensitisation to TDI.

RE: Karol M.H. Concentration-dependent immunologic response to TDI following inhalation exposure. Toxicol.Appld.Pharmacol, 1983 68, 229-241.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (80:20 isomer ratio)

RM: Female guinea pigs, 10 per group, exposed to 0,1,3 or 4 ppm TDI vapour for 3h/day for 5 days.

RS: Two weeks later, serum from each animal analysed for IgG1 and IgE anti-TDI antibodies.

RM: On days 22-30, animals were challenged by exposure to atmospheres of protein conjugates and their respiratory rate measured.

RS: Two weeks after the last exposure, IgG1 antibodies detected in all animals. IgE antibodies in most at 1 & 3 ppm, but only 2/10 at 4 ppm.

RS: Animals with previous TDI exposure showed significant response (increased respiratory rate) when challenged with 'Karol' TDI-GPSA conjugate but not with 'ICI' conjugate. The response pattern for the 'Karol' conjugate was 7/9 of those previously exposed to 1 ppm TDI, 9/10 to 3 ppm TDI and 2/7 to 4 ppm.

RM: Results show detection of antibodies and elicitation of pulmonary hypersensitivity response is dependent upon physico-chemical properties of hapten-protein conjugate.

RE: Botham, P.A, Hext, P.M, Rattray, N.J, Walsh S.T. and Woodcock D.R. Sensitisation of guinea pigs by inhalation exposure to low molecular weight chemicals. Toxicol. Letters 41. 159-173.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Guinea pigs exposed to TDI atmospheres at concentrations of 0.01-5 ppm for 3x6 hours. Respiratory pattern evaluated by plethysmography. 3 weeks later these, and unexposed animals, exposed to approx. 0.02 ppm TDI and respiratory rate measured.

RS: Respiratory rate unchanged at 0.02-0.05 ppm but decreased to 50% at 0.18 ppm and 40% at 0.5 ppm. For animals previously exposed to 2-5 ppm TDI, significant reductions (40%) in respiratory rate occurred when re-exposed at 0.02 ppm TDI. Animals showed skin sensitisation to TDI when patch tested. Guinea pigs pre-exposed to 0.5 ppm TDI and lower did not show greater sensitivity when re-exposed to 0.02 ppm.

RE: Stevens M.A. and Palmer R. The effect of TDI on certain laboratory animals. Proc.Roy.Soc.Med. 1970, 6, 380-381.

5.10 Other Relevant information

Type: Immunotoxicity

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Mature monkeys, macaca mulatta, exposed to TDI atmospheres at concentrations of 0.13-0.7 ppm for 1-3, 6 hour exposures. Breathing pattern recorded by telemetric strain gauge. Some were re-exposed to approx. 0.02ppm for 6 hours. Other monkeys were chronically exposed for periods up to 23x6h exposures at 0.02 ppm.

RS: Animals show acute sensitivity to TDI exposure with lacrimation at 0.4 and 0.7 ppm and a death at 0.4ppm. No effect when re-exposed at 0.02 ppm TDI.
Chronically exposed monkeys at 0.02 ppm showed no effect on respiratory pattern.

RE: Stevens M.A. and Palmer R. The effect of TDI on certain laboratory animals. Proc.Roy.Soc.Med., 1970, 6, 380-381.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (mixed isomers).

RM: Acetylcholinesterase (AChE) inhibition assay by incubation of TDI with human erythrocytes and measuring change in enzyme activity by colorimetric Ellman method. Reversibility of inhibition and spontaneous recovery of AChE activity also investigated.

RS: TDI concentrations producing 50% AChE inhibition were 25µM in erythrocytes and 40µM in whole blood. only slight reversibility of inhibition was shown on washing erythrocytes 3 times. Spontaneous recovery of AChE activity was 28% in 24h. Overall, TDI shown to be potent AChE inhibitor, with maximal effect within 2 min, not quickly reversible.

RE: Dewair M, Baur X. and Fruhmann G. Inhibition of acetylcholinesterase from human erythrocytes by isocyanates. J Occup.Med., 1983, 25, 279-282.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80 : 20 isomer ratio.

RM: Acetylcholinesterase (AChE) inhibition assay by incubation of TDI with human erythrocytes and measuring change in enzyme activity by colorimetric Ellman method. Spontaneous reactivation of AChE activity estimated.

RS: Dose dependent inhibition of AChE activity obtained with TDI. Spontaneous enzyme reactivation was shown to be 90% at infinite time as predicted by a computer program.

RE: Dewair M, Baur X. and Mauermayer R. Inhibition of acetylcholinesterase by diisocyanates and its spontaneous reactivation. Int.Arch.Occup.Environ.Health, 1983, 52, 257-261.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI and 2,6-TDI

RM: Action of the 2 isomers was compared in a series of experiments with Cholinesterase (ChE) from different sources.

a) Titration of purified human serum and eel ChE with the two isomers.
b) Exposure of horse serum ChE to 1ppm atmospheres of the two isomers.
c) Titration of human plasma with the isomers.

RS: a) 2,6-TDI much more potent inhibitor of human serum ChE, than 2,4-TDI, and more potent for eel ChE.
b) Both isomers had similar inhibitory effect on horse serum ChE by inhalation at 1ppm
c) Only small effect on human plasma ChE with increasing dose of either isomer. This may reflect competing reactions with other plasma proteins.

RE: Brown W.E, Green A.H, Karol M.H. and Alarie Y.C.E. Inhibition of cholinesterase activity by isocyanates. Toxicol.Appl.Pharmacol., 1982, 63, 45-52.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI, 80:20 isomer ratio.

RM: Groups of male Sprague-Dawley rats (8 per group) were exposed to TDI vapour in a series of studies -

i) 4 hour exposures at concentrations 0.7 - 4.3ppm

ii) Two 4 hour exposures on consecutive days at 0.7-4.3ppm.

iii) Exposure at 1.2ppm for 4 hours per day for 2, 4, 9 or 14 days.
After the last exposure in each of these studies blood and bronchial tree taken, the latter homogenised, and acetylcholinesterase (AChE) assayed in the samples.

iv) Groups of 5 rats exposed 4 hours per day to 0.3 or 1ppm TDI, 5 days per week for 3 weeks.
After last exposure, lungs excised and submitted to histochemical assay for AChE activity.

RS: Study results, number as above, -

i) No inhibition of bronchial AChE activity

ii) Some inhibition of bronchial AChE activity (19-33%) but not related to exposure concentration.

iii) Some inhibition of bronchial AChE activity (15-38%) but not related to length of exposure.
No effect on blood AChE activity in the 3 studies above.

iv) 0.3ppm did not affect bronchial smooth muscle AChE activity, 1ppm caused a 36% decrease in activity.

RE: Brondeau M.T, Ban M, Simon P, Bonnet P. and de Ceaurriz J. Decrease in the rat bronchial acetylcholinesterase activity after TDI inhalation. J.Appld.Toxicol, 1990, 10, 423-427.

5.10 Other Relevant information

Type: Biochemical or Cellular interactions

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: 2,4-TDI (CAS No.584-84-9), 97.8%.

RM: 10 male guinea pigs exposed to TDI vapour at 29ppb for 5 hours per day for 20 days. 10 control animals air exposed. Animals killed 20h after last exposure and 2 tracheal strips prepared from each animal. Tracheal smooth muscle relaxation and contraction responses to isoproterenol and carbachol respectively were evaluated.

RM: No difference between control and test groups for isoproterenol-induced relaxation. Tracheal strips from TDI animals were more responsive than controls to contraction induced by carbachol. (Mean log ED_{50} of 6.44 compared to 6.23 for control strips).

RM: Authors concluded that TDI has a direct effect on airway smooth muscle.

RE: McKay R.T. and Brook S.M. Hyperreactive airway smooth muscle responsiveness after inhalation of TDI vapours. Am.Rev.Respir.Dis. 1984, 129, 296-300.

5.10 Other Relevant information

Type: Chemobiokinetics general studies

Reference (RE), Remark (RM), Result (RS), Test substance (TS)

TS: TDI (unspecified)

RM: Guinea pigs given TDI or TDI/glycols solvent solution by intractracheal injection at 0.3ml/animal. Other groups of guinea pigs exposed to high concentration of TDI/glycols solution as aerosol (1.2mg TDI/litre) or vapour (0.35-0.55mg TDI/litre). Exposures of 10-20 min at irregular intervals up to 4 weeks.

RS: IT administration resulted in coagulation of proteins in respiratory tract and death from respiratory distress. Inhalation caused asthmatic reactions after initial exposures, leading to dyspnea. Bronchiolitis, pneumonia and emphysema occurred with minimal healing. Guinea pigs sensitised to chicken albumin responded similarly to controls, indicating predominance of a primary toxic effect.

RE: Friebel H. and Luchtrath H. Zur wirkung von TDI (Desmodur T) auf die atemwege. Arch.exper.Path. u Pharmakol, 1955, 227, 93-110.

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